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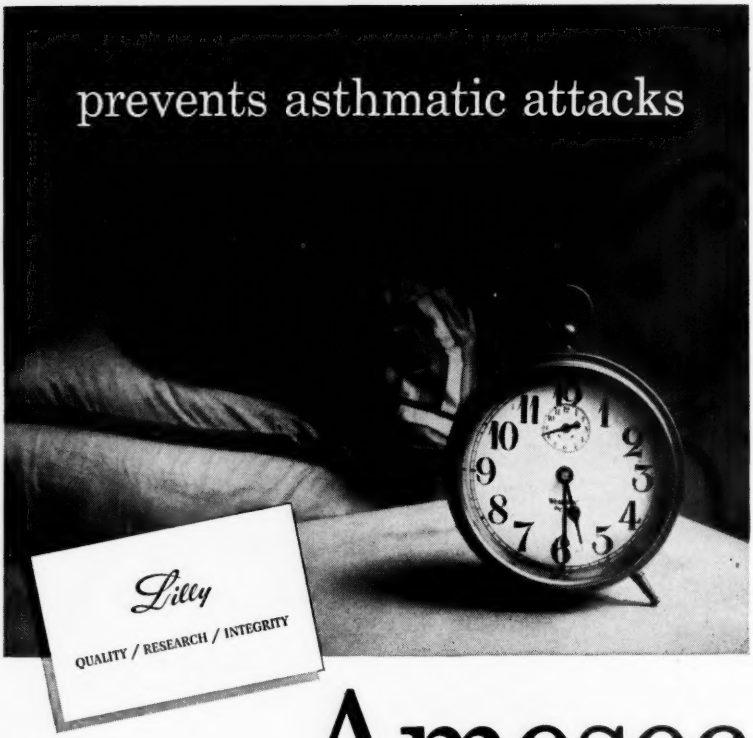

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THE QUESTION OF REACTIONS TO MERCURIAL DIURETICS

A Reappraisal

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TREATMENT directed towards the control of edema has become increasingly routine during the last decade, chiefly because of a better understanding of the physiology and pathology of the edematous patient, the availability of safe and effective medicinal agents, and, as well, the knowledge as to how they should be used. Because our population is increasing in average age, we can anticipate a growing incidence of the disorders generally requiring treatment with diuretic agents, and particularly with the mercurials, because, today, it is considered that "not only are they the most reliable diuretic agents, but also the most powerful."[51,65] Moreover, as Kossmann[64] has recently pointed out, "the man or woman with the failing heart lives a very much longer time," a fact which he ascribes to the sodium-restricted diet and the advent of nontoxic mercurial diuretics. It is therefore necessary to correlate what we know of the actions and reactions of the mercurial diuretics with what has been learned in other fields of medicine.

Allergic reactions to these drugs have been noted in the literature, and will inevitably become more common as the courses of treatment lengthen. Of the patients undergoing long-term diuretic therapy, an increasing number are also our asthmatic and otherwise allergic patients. We find ourself, therefore, gradually working more and more with the cardiologist, combining our knowledge of allergy and drug reactions with his of cardiac disease. In considering the patient with a reaction to a diuretic, and in managing the allergic or asthmatic patient who is also on diuretic therapy, the complex subject of diuresis becomes increasingly significant to the allergist. Armed with this understanding, the techniques

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of accomplishing maximum therapeutic effectiveness and minimizing the possibility of untoward reactions are not complex.

While promising progress has been made in the science of diuretic therapy, much of our knowledge concerning fluid imbalance and its correction remains empirical, since there is only rarely a one-to-one correspondence between causes and effects. To no other bodily affliction is Wilde's epigram more pertinently applied, in that the "truth is rarely pure, and never simple." Everything we do know points to the fact that the total patient is affected by diuretic therapy, and to a greater degree than in almost all other disorders and their treatments. Evidence points to renal tubule action, but equally important extra-renal factors include psychosomatic elements, enzyme action sequences, trace elements and hormone imbalance,[78] all kept in balance by subtle, complex and interrelated metabolic systems.

Sodium and potassium are known to be important in water retention, but so is ferritin, a newly identified and as yet little understood vasodepressing agent. The concatenated pathologic mechanisms quickly affect the entire body to the degree that a disorder which can begin in any one of a group of organs is rapidly reflected in all of the others. Modifications soon occur in the lesser circulations, not only of the central organs, such as the heart itself, but also of the kidneys and the liver, and more distantly, one might say, of the hydraulic systems of the pulmonary and peripheral circulation, and lastly, in the tissue cells.

Whether the patient is male or female, bedridden or ambulatory, ill during the summer or the winter, will all affect his reactions to these special drugs. Ben-Asher, for example, notes an association of reactions to the mercurial diuretics when environmental temperatures are high at the time of injection.[6] The dosage relationships are not simple, since Moyer et al have shown that at small dose levels there is a high sodium output in relation to water, while with greater doses the water output is proportionately increased.[75] Others have similarly shown that there may not be a constant relationship between sodium loss and water output.[71,101] Similarly, the degree of the illness of the patient is a factor. Those patients grouped as Classes I and II, Congestive Heart Failure, react quite differently from Classes III and IV.

Faced as we are with this holistic situation, it is not surprising that there are many questions, and that all the answers are not yet known. In the state of such partial knowledge, it is understandable, but unfortunate, that so much of what is written on the subject of diuresis is founded on traditional misconceptions. In the available literature there is a need to separate the reactions properly ascribed to the mercurial drugs from, on the one hand, those reactions more properly due to the patient's biochemical individuality in health and in illness, and on the other, from the so-called "reactions" which are actually the result of the type of

treatment in use. It is essential to distinguish the reactions due to diuresis —especially when the diuresis is allowed to become excessive—from reactions to the drugs themselves.

In the case of the mercurials, current attitudes and conclusions can frequently be traced back to earlier data derived from experiences with bichloride of mercury and calomel. The opinions of some workers are derived from results of treatments with Novasurol®* and Esidron,® among the first of the modern mercurials, and drugs of "notorious toxicity,"[105] which have long been withdrawn. The intravenous route of administration of these older drugs was associated with toxic effects. Such experiences have been projected forward and applied to the newer organic mercurial complexes, administered by other routes, as though it were possible to obtain the optimum therapeutic results using today's medicines with the techniques of yesterday. In this frame of reference the antecedents of the problem are not really important. Inherently the problem itself determines the pattern of its solution.

This background material made it appear useful to review the major published work of the last few years. A review of this type attempts to re-evaluate the reactions to the currently used mercurial diuretics in the light of present knowledge. If reactions can be avoided, or if and when they occur the reasons for their occurrence can be made less obscure, such a review will incidentally serve as a guide to the more effective use of these medicinal agents in specialist and general practice.

PROBLEMS OF EVALUATION

We know generally that the mercurials are potent diuretic agents, which makes it all the more important that we reassess—as far as is possible from the available data—the evaluation of their possible toxic effects for any particular patient. In this regard, a number of points must be clarified if we are to use these drugs with maximum safety and efficacy.

Although many papers concerned with reactions to mercurial diuretics have been written, the available literature leaves much to be desired in terms of adequacy and precision, terminology, and statistical evaluation. It should be noted, in defense of those workers who have tried to bring some semblence of order into this field, that many of the variables could

*For the sake of uniformity, the designations of the more common mercurial diuretics have arbitrarily been changed, as far as possible, to the more familiar trade names. The equivalent generic terms are given in the following table for reference.

1.	Cumertilin®	—mercumatilin
2.	Mercuhydrin®	—meralluride
3.	Mercupurin®	—mercurophylline
4.	Mercuzanthin®	—mercurophylline
5.	Neohydrin®	—chlormerodrin
6.	Salyrgan®	—mersalyl
7.	Thiomerin®	—mercaptomerin

not always be isolated. Some of the facts we would like to know about the reactions to these drugs cannot always be objectively measured.

However, much of the published material consists of case reports based upon experience with relatively small groups of patients. With the complex variable factors involved, conclusions based on such small series are always susceptible to the subjective attitudes of the observer. The fact that we are dealing with so very intricate a system of responses makes precision and controls imperative, that is, if we want to be definitive. When this is experimentally unrealistic, then we need larger groups of subjects. Some of the variables, such as differences in drugs, dosage forms, duration of treatment and differences in the disorders and conditions of the patients—to name but a few—could then be studied and statistically validated.

THE PATIENT OR THE DRUG?

It is important, though not simple, to differentiate between reactions due to inherent properties of the drug, and those more properly ascribed to the patient and to his disease and treatment.

Much of the confusion noted in the pertinent literature is due to the fact that, as is true in so many other cases of chemotherapy, we are dealing with substances which, in measurable quantities and identifiable chemical forms, may play a role in healthy human physiology. Mercury is present in our food, and a normal daily diet has been found to contain about 20 μg.[39a,90] It travels to and is deposited in many body tissues in amounts which vary from individual to individual and organ to organ.[49]

Forney and Harger studied ninety-two patients who had taken no known mercury medications, and found concentrations up to 12.7 mg/100 gm of kidney tissue.[35] Using the latest and most precise spectrographic techniques on the kidneys of subjects who had no record of having received mercury, Griffith et al, in a study of 910 autopsied patients, the first sufficiently large series to give us standard data on metallic content of human tissue, found an average mercury content of 2.05 mg/100 gm of dry tissue.[49] Mercury, or mercury compounds derived from either food or from chemotherapy, appear similarly to be retained or excreted.

The majority of patients, it appears, can tolerate without untoward effect a therapeutic dose of a mercury compound.[41] Griffith et al studied patients who had received an average dose of 4,692 mg of mercury over periods ranging from three weeks to forty months, and found that, although there was somewhat more mercury in their kidney tissue than in the tissues of nontreated patients, the evidence indicated that this was not associated with either kidney disorder or rising nonprotein nitrogen levels of the blood. On the basis of this evidence, they conclude that "small and massive doses (of mercurial diuretics) are not injurious in the absence of anuria due to hyponatremia."[49]

Obviously, some individuals will present an idiosyncrasy to mercury, so that either initially (or after becoming sensitized) they may respond abnormally to its presence. Presumably, this may be as true of dietary as it is of chemotherapeutic mercury. In some cases, the patient's reaction is obviously quantitatively related neither to the source of the mercury nor to its amount. In others, reactions are seen only after really prolonged use, and may be the result of sensitization. Gold et al report what they consider "evidence of acquired allergy" in approximately 16 per cent of 209 patients given subcutaneous Thiomerin.[42] Incidentally, they are of the opinion that these reactions to Thiomerin may be attributed to the "thiol" portion of the compound rather than to the mercury component.

If reactions are to be considered the result of cumulative effects, they must be related to the fact that patients get into difficulties if and when mercury is introduced into the system at a faster rate, that is, in greater quantities, than they can, at the moment, handle. Speed of administration alone may, therefore, result in toxic pericellular concentration levels. Since this is true of many other drugs, the question is always raised and then answered on the basis of the limits of tolerance to the particular medicinal agent used, its biochemical properties, its route of administration, its rate of absorption, its concentration in the circulation and in and around the tissue cells, and its excretion.

Under these circumstances, the term "hypersensitivity," venerable though it may be, has no useful meaning, since the term connotes *every* type of reaction. Those who use the term most frequently are rarely familiar with the basic literature concerned with reactions, and do not, therefore, use the known well-defined, specific and exact terms. There are any number of sources for the exact vocabulary to be used for describing drug reactions.[15]

Not all of the patient's symptoms are necessarily due to the diuretic, but may well be the result of the diuresis itself, however obtained.[27,58,97] Copious diuresis and hemoconcentration may, for example, in some patients cause the characteristic symptoms of over-digitalization, although nausea and vomiting may be common both to this state and to some mercurial effects. Excessive diuresis may result in ionic imbalance, associated with muscle pains, convulsions and coma.

Important in the patient-drug relationship is the fact that many of the fatalities attributed to the injection of mercurial diuretics may be due to other causes. Kaufman, in 1948, reviewing twenty-three years of published literature, uncovered only thirty-two reports of fatal cases, all of them following intravenous therapy.[60] The author himself notes that "time relations, moribund condition of the patient, and other factors, leave room for doubt about the role of the mercurial." Reviewing critically Kaufman's cases, Ray and Burch observe that not only was the administration intravenous, but that large doses were given to patients

with pre-existing nephrosis and nephritis, and that, in most cases, there was an ominous record of previous intolerance to the drug.[80] These authors, as well as Dicker,[26] point out that many reported fatalities occurred in children who were given doses now known to be excessive. Stanley's report[94] in 1949 describes 27 fatalities, all but one of which were included in Kaufman's review. Of these twenty-seven cases, nine suffered from congestive heart failure, four from nephritis, four from arteriosclerosis, three from rheumatic heart disease, three from nephrosis, three from myocardial infarction, three from hypertensive heart disease, and the others from as varied a series of disorders as angina; congenital, syphilitic, postrheumatic and thyrotoxic heart disease; diabetes; tabes dorsalis; ventricular aneurysm; pulmonary infarction; cirrhosis of the liver; and myxedema. In fourteen of these patients, autopsies were done, and no immediate cause of death was uncovered. Eight died immediately, and the remainder within one to five minutes. In ten, cyanosis was the first symptom noted; in seven "gasping"; and in eight more, dyspnea; while in four there was "respiratory difficulty." Five went into immediate collapse, and five others into convulsions. Three suffered from ventricular fibrillation, three from cardiac irregularity, and three from tachycardia, one from bradycardia, and one from "cardiac standstill." In two patients there was vomiting, and two more were noted as having flushing of the face. The laboratory and physical findings were equally variegated.

In these cases, death may have been due to rapid injection, causing "speed shock," especially since the intravenous route of administration had been used in twenty-six of the twenty-seven patients. In some of these patients, there may have been an immediate "toxic" effect upon the heart. The sympathetic system may have been paralyzed.

Kaufman's and Stanley's series include seven previously described by Wolf and Bongiorno.[104] To choose one of these cases for more detailed description, four injections of Salyrgan® were taken with no ill effect. The fifth was followed by chills and fever, and a morbilliform eruption. The sixth injection, given seven days later, was followed by shock and sudden death. On the other hand, another patient in Stanley's series reported upon by Wexler and Ellis[103] received Mercupurin in a total dose of 164 cc over a period of eight months. The penultimate treatment caused apprehension and dyspnea, the next injection, death.

Although of Stanley's twenty-seven cases, death occurred in four with the first administration of a mercurial diuretic, it should be stressed that fair warning had been given, in that in seven others previous reactions had taken place. The reports do not list this information for four of the patients, but the complete absence of previous reactions had actually been noted in twelve. In nine patients, death followed the use of Mercupurin; in seven, Salyrgan; in three, Neptal; in two, Salyrgan-Theophylline; in one, diluted mersalyl; and in the others, diluted Neptal. Eighteen of the

patients received a dose of 2 cc; four more were given 1 cc, and one patient, 3 cc.

In those patients in whom there was a rise in temperature or a rash, a sensitization process can be postulated as having occurred. Why it occurs when it does, we do not know. A patient described by Wallner and Herman took with safety a daily dose of 2 cc of Mercuhydrin.[99] Following the eighth injection there was a temperature rise to 102° F. A diffuse erythematous rash appeared on the tenth day of treatment. The temperature and skin returned to normal with cessation of diuretic medication. This was resumed on the eighteenth day, with 2 cc of Mercuhydrin, given intravenously. The patient went into shock, and died several hours later.

In the published report, there is some doubt as to whether Higgins' patient was or was not so sensitized.[56] Intravenous and intramuscular Salyrgan and Mercupurin were apparently tolerated for three months. Following intravenous injection, there were chills and dyspnea. Two weeks later an intramuscular injection of 1 cc of Mercupurin caused not only chills and fever, but hypopiesia, dyspnea and prostration.

There is, however, no doubt of a typical sensitizing process in a patient described by Fineman and Rosenberg.[31] On the eleventh day of a first course of treatment with Mercuhydrin, there were chills and fever. These occurred three days after the initiation of a second course of treatment, and then, during a third course, appeared fifteen minutes after the first injection.

Finally, in consideration of these serious and fatal reactions that have, in the past, been attributed to diuretic drugs, it should be noted that in the newer literature reflecting the growing awareness of the factors involved, one finds an acknowledgment of the fact that "over-enthusiastic efforts to rid the body of sodium may result in serious or even fatal electrolyte depletion."[97] Similarly, we now possess the benefit of case reports on fatal reactions attributed, not to the drug used, but to "a regimen of sodium restriction combined with vigorous diuresis,"[57,91] or, as in another report, to renal failure "due to low extracellular sodium chloride."[86]

A similar awareness of the difference between the results of diuresis and the action of diuretic drugs *per se* is reflected in the recent discussion of this subject by Krantz and Carr, who point up the fact that many of the symptoms hitherto attributed to the diuretic drugs actually reflect problems of management, and are thus "the result of the intended action of the drug, and not an untoward side effect."[65a]

These all add up to the important dictum that it is rarely the *drug* which is administered, but always the *total* patient who is managed. The determining factor is actually not either the drug used for treatment or the disorder treated, but the skill and judgment of the physician.

FREE ION VERSUS ORGANIC COMPLEX

Inorganic mercury salts are known to ionize freely, and *their* systemic action is clearly the result of the properties of the free mercury ion. As for the organomercurial diuretics, from their very inception, as noted above, the question of whether they acted in terms of the free ions or as the intact organic complexes, has been the subject of much speculation and some investigation. Saxl and Heilig, in their pioneer study of mercurial diuresis, ventured the opinion that it was "not the mercury action, but the specific organic molecule" which was responsible for the diuretic effects.[85] There was a subsequent tendency to ascribe the pharmacologic effects of mercurials, as Vogl expresses it, to a "reversible toxic effect of the mercuric ion."[105a] More recently, however, there is evidence that pharmacologic thought has made a full spiral, and is returning to the point of view ascribing the action to the organic complex. This newer viewpoint is reflected by the statement in the recent edition of the Goodman and Gilman textbook that, "Older evidence suggested that the organic mercurials were active by virtue of their release of mercuric ion (Hg^{++}). However, it is more likely that organic mercury complexes dissociate as such and act in the form of $R\text{-}Hg^{+}$."[46]

The conclusion that ionizable, or ionized, mercury is the active ingredient of these organomercurial complexes would seem to be directly contradicted by the fact that those compounds which are most unstable and ionize most freely, are diuretically the least active.[48,52] Under experimental conditions, since the effects of these compounds which ionize to greatly differing degrees vary so markedly, even though they are ingested and excreted at the same rate, they apparently (molecule for molecule) act differently. Rowland found that, in rats, the toxicity of the various organic mercurial complexes was not a direct function of the degree of ionization.[83] Many of the newer organic mercury complexes, although kept in solution for long periods of time, do not ionize. Grollman states that "The organic mercury compounds do not dissociate to give mercuric ions."[50] In fact, the N.N.R. specifications for Neohydrin,[20] for example, explicitly state, in the discussion of the tests for this drug, that there be "absence of ionizable mercury and other heavy metals, as indicated by the standard sodium sulfide reaction."

Basing his conclusion on the best available evidence, Smith says, "It seems probable, therefore, that their natriuretic action (of the mercurial diuretics) is attributable to the properties of the organic complex *as such.*"[92] Although, to date, studies have not yet definitively established the diuretic action as due to the organic complex, Kolmer says that a mercury complex may be absorbed and excreted *as such,*[63] and it is the opinion of Handley, based on work in progress, that "the mercurials are excreted as the original compound, and that mercury is not split off."[54] He notes further, "although these observations do not prove that the diure-

sis from mercurials is due to the intact molecule, it strongly suggests that such is the case."

The notable exception is Thiomerin, which in aqueous solution reportedly decomposes rapidly and does release free mercury ions. With this one exception, it is therefore not valid to assume that we are dealing with the toxic properties of free mercury when we are discussing organic mercurial compounds. It is apparent, from the experimental studies, that these organic complexes possess highly selective actions upon the enzyme systems involved in diuresis. Organic mercurial complexes differ so greatly that they affect the enzyme, succinic dehydrogenase, in different parts of the renal tubules.[77] It is plausible and safe to assume that the differences between the newer and the older drugs, and between the newer drugs themselves, may well be due to the specific nature of the intact organic complexes involved.

MODE OF ADMINISTRATION

In any evaluation of the reports of reactions to mercurial compounds, it is always important to stress the method of administration. As noted above, the serious reactions have, almost without exception, followed intravenous injections. Mercuhydrin was the first of these drugs with local irritant action sufficiently low to make the intramuscular route acceptable, and this method of administration has since become increasingly widely used.[41]

Reaction to intravenous administration does not mean that the same drug cannot be used either intramuscularly or subcutaneously. Indeed, there are recorded cases in which the change from intravenous to intramuscular or to subcutaneous administration has apparently eliminated any untoward reactions.[16,47,70,99]

However, an unfavorable reaction to intravenous administration may be followed by an equally or more serious reaction to the intramuscular injection of the same drug.[56] In these cases it would appear that the dose and the time between the injections may have served to sensitize the patient to a greater degree, so that severe reactions followed the injection of the more slowly absorbed compound. In such patients, one may also conclude, above and beyond increased sensitivity, that the reaction is to the specific molecule rather than to the hypothetic mercury ion.

In this connection, it should be noted that in patients in whom the intravenous injection, for example, of Mercupurin, was followed by a severe reaction, a similarly severe effect followed the use of the same drug in the form of a rectal suppository.[61] This may not be as different a method of administration as it appears, since rectal absorption can be quick, and in any case, may bypass the liver.

In this same regard, it must finally be noted that the introduction of effective oral diuretics involves not only a matter of convenience, but

also a slower rate of absorption and a more readily controlled dosage schedule. Accordingly, the reactions following *oral* mercurial diuretics must be evaluated, not only in the light of the particular organic complex involved, but also in view of the fact of administration *by mouth.*

FATE AND EXCRETION

Mercury, as derived from the diet or from chemotherapy and entering the circulating blood, probably forms a complex with plasma albumin.[102] In the case of the organomercurials, the available data do not indicate conclusively whether this reaction takes place with ionic mercury or with the organic mercurial complex. The configurations of the latter would point to the fact that they are not haptogenic. As indicated above, recent work would seem to suggest that the organic complex remains intact in the system. Milner's experiments, however, indicate that the amount of organic mercury bound is a function of the concentration.[72] When the diuretic is present in a dilution of 1:1000 or greater, more than 90 per cent of its mercury content is bound. When the concentration is 1:100 or less, more than 50 per cent of the mercury content may be free.

Bound or unbound, mercury and mercury compounds leave the plasma rapidly and are widely distributed throughout the tissues of the body, being present in measurable quantities in almost every organ, including bone. As previously noted, significant amounts of mercury are found in the normal kidney.[42] The storage equilibrium is affected by pH, with the amount stored increasing *pari passu* with higher pH values.[65b]

The greater part of the ingested mercury is actually eliminated during the first six hours following ingestion. Ray and Burch,[80] using radioactive tracer techniques, report rapid excretion of a mercurial diuretic administered intramuscularly, and, of course, more rapid excretion following intravenous injections.[90a] With intravenous Mercuhydrin, as much as 98 per cent can be recovered from the urine within twenty-four hours.[53] With Thiomerin, the excretion is as high as 90 per cent. In patients with congestive heart failure, individual variations can be great, the rates overlapping those seen in control subjects. The state and phase of the heart failure naturally influences the rate of excretion. Renal impairment may be so advanced as to result in an extra-renal accumulation of the drug, more than enough to exceed the thresholds of toxicity. Unhappily, these factors have not always been taken into account in the reporting of "reactions" attributed to mercurial diuretics.

Combination with theophylline increases the rate of excretion. When mercurials without theophylline are injected intramuscularly, as much as 20 per cent of the drug remains localized at the site of an injection for as long as forty-eight hours. With theophylline added, absorption may be almost complete by the end of one hour.[22] Theophylline salts will also apparently reverse so-called "resistance" to mercurial diuretics. In fact,

choline theophyllinate will both *increase* the diuretic response of the mercurial and *decrease* the need for frequent diuretics.[4a] Tolerance to such "reversal effects" is rarely seen.

DOSAGE AND MANAGEMENT

We should always remember the obvious fact that, with mercurial diuretics, as with any therapeutic agent, overdoses can produce toxic and sometimes fatal effects.

Dicker emphasizes the importance of dosage, and criticizes the practice of accepting 1 or 2 ml of the mercurial compounds as a "standard dose." He points out, "If the dose had been calculated on the basis of mg/kg as it should have been, it would have been realized that the dose administered to children is the equivalent of 6-8 ml in an adult."[26]

A number of observers have advised the use of small initial doses.[33,43,76] The phenomenon of "conditioning" is relevant in this discussion, since it is commonly true that a small initial amount of many medicinal agents may give the patient increased tolerance for larger subsequent doses.[15] Early in the history of mercurial diuretic therapy, Crittenden noted that the administration of small amounts of Salyrgan or Metaphen® enabled experimental animals to tolerate doses of a magnitude which might otherwise be toxic.[21]

Results of overdiuresis and other problems arising from the management of the patient must be distinguished from reactions to the properties of the drugs, a subject which is discussed at length below. In this connection, it is relevant to recall the observation of Donovan et al that while, in an emergency, an ideal diuretic should produce a rapid diuresis of short duration, the same diuretic might not be desirable when slow, smaller diuretic effects are needed. On the other hand, agents for maintenance treatment may initiate a slow, but ideally provoke, diuresis of relatively long duration. They note, in this connection, that Neohydrin, because of its readily adjustable dosage schedule, has, in their experience, markedly lessened the incidence of untoward reactions.[28]

HOW DIFFERENT ARE THE DRUGS

In discussion of the mercurials, the statement is frequently seen that the individual drugs do not really differ very much, one from the other. This tendency to group drugs, as, for instance, vitamins, antihistaminic and antibiotic agents, into generic classes, may sometimes be a matter of convenience. Unfortunately, it often leads all but the most careful clinician into habits of thinking in terms of loose generalizations.

OLD VERSUS NEW DRUGS

The literature confirms the observation of Pitts and Sartorius that "all organic mercurial diuretics are not equally benign." The older of these

drugs, Novasurol and Salyrgan, as they point out, are organic diuretics of high toxicity.[77a]

We have noted the fact that in many of the papers concerned with the subject of treatment with mercurial diuretics, the inference is drawn that some relationship exists between what we see today and what was seen in the days of the inorganic compounds, bichloride of mercury and calomel. Historically speaking, it was the toxic properties of these drugs which stimulated pharmacologists to search for new mercurial compounds, aimed originally at the treatment of syphilis. Incidental to this research was the observation that the mercurials possessed diuretic effects and possible use in congestive heart failure. This discovery, confirmed by clinical studies, in turn stimulated further pharmacologic investigation. This was followed by the development of a series of new and better mercurial compounds, and with them a shift from the intravenous to the intramuscular, subcutaneous, and, finally, oral routes of administration.

THE NEWER AGENTS

These newer drugs are, all of them, organic complexes, in each of which mercury is combined quite differently, giving each distinctly unique properties apparently unrelated to the parent molecules or to each other.

Among the currently used mercurial agents, including those which most seem to resemble each other, there are significant differences. The evidence mounts that each acts as a complex unit, with its own particular properties. It is common to discover tolerance to one drug in a patient who cannot, at all, tolerate another.[37,40,73,105b] Slight chemical differences cause marked therapeutic variations. Knowledge in this part of the field of mercurial therapy can only be organized if simple generalizations are avoided, and the differences between the various organic mercurial compounds are studied, so that the techniques of their use in patients can be improved.

In support of this statement, it is known, for instance, that the differences in activities of these compounds are not directly related to their so-called equivalent mercury content. Fourneau and Melville have pointed out that the activity of the newer mercurial drugs is not in direct relationship to mercury, but to their chemical linkages.[36] As compared with the older mercurials, the more efficient of the newer drugs produce a comparable diuretic effect with a considerably lower mercury equivalent.[65c]

Handley et al, in their pharmacologic studies, found that on a mercury equivalent basis Neohydrin given intravenously to animals was three to four times as active as Mercuhydrin, and that the rates of excretion of Neohydrin and Mercuhydrin are significantly greater than those of Thiomerin.[52] Mayer et al also comment on "the wide range of diuretic potency" exhibited by the different compounds in their clinical studies.[74a]

Using Mercuhydrin injected intramuscularly as a standard, and the

dosage-response curve as a technique for measuring diuretic activity, Gold, Greiner et al have shown great and graded variations to exist, although the compounds studied possessed comparable "mercury equivalents."[48] In a comparison of six preparations, adjusted to a mercury content of 40 mg/cmm, DeGraff and Lehman confirm th marked differences in diuretic activity.[23] Indeed, in connection with t r bioassay studies of diuresis, Gold, Greiner et al point out "the significance of the common expression of relative potency of organic mercurials in terms of mercury content is open to question."[48] It cannot be said too often that these are different chemical complexes, dependent for their action on their individual properties.

The differences in toxicity, also with dosages of equivalent mercury content, are further evidence of the unique properties of these compounds. Blumberg et al reported Mercuzanthin to be distinctly more toxic, both locally and systemically, than was either Cumertilin or Mercuhydrin.[10]

Pitts and Sartorius state that "Mercuhydrin is less toxic locally than other theophylline-containing organic compounds," and that Salyrgan-Theophylline and Mercupurin are too irritating to be injected by any route but the intravenous or intramuscular.[77a] Barrett, in a study comparing effects of Mercuhydrin and Thiomerin in dogs, concluded that "Thiomerin appears to be more nephrotoxic than Mercuhydrin."[3]

In a study of eight diuretics given orally, four of them mercurials, Greiner and Gold found an effectiveness-toxicity ratio that varied in the case of mercurials from seventy-eight (Mercuhydrin with ascorbic acid) to 284 (Neohydrin). They conclude, "There are marked differences between the various diuretic agents given orally when they are examined for the diuretic effectiveness in relation to the corresponding incidence of gastrointestinal irritation."[47a]

Finally, and perhaps more basically, there is now evidence that the newer mercurials act very selectively at demonstrably different sites. Mustakallio and Telkka have shown that Mercuhydrin inhibits the whole proximal convoluted tubule; Thiomerin, the middle part; Esidron, the straight terminal portion, and Neohydrin and Salyrgan, the straight terminal portion, excepting for the lowest part, which is inhibited by Mercuzanthin.[77]

This and similar evidence controverts the often repeated statement that mercurial diuretics are "all the same." It would seem to support the point of view that the action of these drugs is not directly related to the mercury equivalent, but rather to other properties of each particular complex.

It is important, therefore, in evaluating the currently used drugs, not only that we do not confuse them with the older inorganic mercurials, but that, equally important, we separate the newer organic salts of the last few years from the transitional drugs of ten years ago. Finally, the very newest organic mercurial compounds must be kept distinct, one from another.

REACTIONS TO MERCURY: MERCURIALISM

Our spontaneous reaction to the term "mercurial" is inevitably related to mercurialism, which properly designates the type of toxicity with which physicians were familiar before the introduction of the newer organic mercurial salts. The inorganic salts of mercury, used for centuries, freely ionized into either the mercurous or the mercuric ion, and yielded the characteristic symptoms of acute mercurialism.[19] Stomatitis, tender gums, excessive salivation, swollen tongue, fetid breath, oral ulcers, and the development of the "blue line" were all seen. Nausea, vomiting, tenesmus and bloody diarrhea occurred. Signs of renal involvement, ranging from albuminuria and hematuria to severe toxic nephrosis, with extensive tubular epithelial necrosis and glomerular damage, with intermittent or continuous suppression of urine, uremia and death, are the significant findings. This is the familiar pattern in poisoning from such drugs as bichloride of mercury. It continues to be seen sufficiently often to be well known to medical examiners. Gonzales states that it is seen in suicidal deaths due to mercuric chloride at the rate of approximately twelve cases yearly, and in accidental or undetermined deaths due to mercury, in probably six more. He continues, "Poisonings from organic mercury compounds are rare,"[45] and very seldom seen is "neurotoxic" chronic mercurialism.

Especially in the older studies of mercurial diuretics, there is a tendency to relate the observed reactions of mercurial diuretics to the classic "mercurialism." It should be pointed out that this involves several assumptions. In the first place, it assumes that the drugs ionize readily and liberate free mercury, a fact certainly not true of the newer organic mercurials, which, if they do so at all, ionize very slightly and slowly. Indeed, there is growing evidence, as previously noted, that they act as intact organic complexes. Furthermore, one would have to assume that mercury, normally present in human tissue, is present in quantities, or introduced at a rate greater than can be handled by the body. But the therapeutic index of any potent drug is similarly a function of dosage and management. All therapeutic agents are useful at one level, and potentially harmful in excess. Finally, the frequent statement that the effectiveness of these drugs is related to a "toxic effect" in the renal tubules is misleading, since all of our chemotherapeutic agents are toxic in the same sense, and it is their very selective toxicity at controllable levels which makes them useful.

If one of the older drugs which did ionize rather freely is given to a patient who does not "diurese" well, and therefore accumulates the products of the ionization, and if again the patient is unusually sensitive, if not idiosyncratic to mercury compounds, the stage is then set for the type of serious reaction that was reported (often as mercurialism) in the earlier literature concerned with Novasurol and Salyrgan. Such reactions are not seen today.

On the other hand, laboratory studies previously discussed show that

the activity of the newer drugs is related to their properties as organic complexes, and not to the presence of free mercury. In experiments with dogs, evidence of mercury poisoning is absent, as when Handley et al studied the effects of massive doses of Neohydrin, and reported no evidence of mercury poisoning, the autopsy studies of the kidney, heart and lungs showing no difference between the control groups and those receiving the drug.[53]

That this may not be equally true of all mercurial organic complexes is suggested by recent studies done with a mercurial diuretic agent in which a mercaptide complex replaced the theophylline. Barrett reported that with Thiomerin, in dogs, after five days of a 3 mg dose equivalent of mercury per kilogram of body weight, a mild albuminuria was produced. In other dogs, with a dose of 7 mg of mercury per kilogram, there were clear-cut signs of renal failure. On the other hand, with Mercuhydrin there was no overt evidence of renal damage when daily doses as high as 9 mg of mercury per kilogram were given.[8]

Turning to human studies in normal individuals who have taken no mercury, it can be seen what high tolerances for this element exist. In the previously cited study by Forney and Harger, of patients who had taken no known mercurial medications, substantial concentrations of mercury were found in kidney tissues. Microscopic evidence of pathologic changes of the type associated with mercury poisoning, was lacking.[35]

The ultimate test is bioassay: how these drugs act on large numbers of human patients.[14] When subjected to this test, we find that the symptoms of true mercury toxicity are actually not seen as often as the reactions following overdosage from many common medicines.

The present author would want to be the last to say that any substance capable of affecting the human organism could not, under appropriate conditions, be either allergenic or toxic. Nor, going to the other extreme, would he want to say that these mercurial diuretics are as innocuous as is aspirin.

In overdosage, toxicity occurs, and in a special group of patients to be described, allergic and other reactions are seen, but the fact of the matter is that the newer mercurial drugs, used correctly, are not properly associated with the classic manifestations of mercury toxicity, a conclusion amply supported by both laboratory and clinical investigation.

REACTIONS TO NEWER MERCURIALS

The literature abounds, and is well documented, with reports of patients who, for many years, have received many injections of these drugs, with no evidence of major toxicity. There are records of patients who have taken as many as 627 injections over a period of twelve years,[38] total dosage as high as 1500 cc having been given without any evidence of mercurialism or any known lesion in the kidney.[87] Fineberg has reported

on a patient who received 343 injections over a period of seven and a half years, without any deleterious effects.[30a] For the effects of long term mercurial diuretic administration, without renal damage, the patients studied by Forney[34] and Schroeder,[87] and those by Moyer, Handley et al[76] are also prime examples. One of the author's own patients took weekly injections for more than ten years, with no adverse effects (unpublished data).

Gold reports on patients with congestive heart failure, some of whom received 2 cc of a mercurial diuretic two or three times weekly for periods of six months to three years.[43] He has a series of three patients who received a daily dose for periods of from two to three years, thereafter presenting no evidence of renal damage. In the series presented by Finkelstein and Smyth, there were 206 patients who were given 1070 injections at intervals of four to seven days, none presenting toxic kidney effects.[32] "No indication of renal injury after the organic mercurials were given intravenously at weekly intervals over periods up to five months," was reported by Modell et al.[73] Gold and his colleagues followed 140 patients, treated up to two years with Mercuhydrin, and reported, "We have found no convincing evidence of renal injury." DeGraff and Nadler have noted that 6000 injections of mercurial diuretics a year, for eight years, were administered at Bellevue Hospital (New York) without serious toxic reaction or death which might be attributed to the drug.[24] And finally, in a recent report, the experience of one hospital group has been cited, in which more than 13,000 injections of mercurial diuretics were administered over a period of four years, with no untoward effects.[67a]

A study of the individual types of reactions might be rewarding, especially if we return to a discussion of sensitization phenomena. The following types of reactions are not given in order of importance, and the classifications are not mutually exclusive.

PAIN AND OTHER LOCAL REACTIONS

When mercurial diuretics are injected, local reactions may occur. These may appear after several hours, but more frequently they are not apparent for several days. Those mercurial diuretics compounded with theophylline are less reactive locally, as well as systemically, although among these same compounds there are significant differences.

Modell et al have made an extensive study of this problem. Either Mercuhydrin or Mercupurin was injected at weekly intervals into the gluteal muscles of thirty-nine patients. Mercuhydrin was less painful in 60 per cent of the patients. No difference was noted in 26 per cent, and Mercupurin was less painful in only 5 per cent of the cases. These subjective patient reports were confirmed in a blind test, which established Mercuhydrin injections as less painful than the Mercupurin.[73]

Finkelstein and Smyth concurred with Modell's observation that Mercuhyrin caused less local irritation on intramuscular injection. They record pain at the site of injection in only seven of 234 intramuscular injections.[32]

Warshaw et al also report that when Mercuhydrin is injected deep into the gluteal area, pain is usually negligible and signs of local irritation are rare.[100]

In a study of two separate series of over 100 patients given each drug, Atkinson and Mulligan discovered that injections into the deltoid muscle produced considerable discomfort in 12 per cent. On the whole, following deltoid injections, Mercuhydrin seemed to be less painful than Thiomerin. But with each of the two drugs, injections into the gluteus maximus produced reactions in about 5 per cent of the patients.[1]

It has been stated that Thiomerin might be given subcutaneously, and perhaps by self injection, without local irritation.[13,29,66,84] However, in a study of patients given prolonged intensive treatment, Gold et al noted that in 44 per cent of the patients receiving Thiomerin there were local reactions, including pain, inflammation, echymoses and fibrous nodules.[42] Atkinson and Mulligan reported "considerable discomfort" in 35 per cent of 140 cases, and "mild discomfort" in 12 per cent given Thiomerin subcutaneously.

Sussman and Stein report that in more than 1000 injections of Mercuhydrin given subcutaneously, there were no local reactions and only a brief stinging sensation.[95] Using the same drug, also given subcutaneously, Koffler and Brenner noted marked to severe pain in only six of 217 injections.[62] In a series of 200 patients given 1132 subdermal injections of Mercuhydrin, Warshaw et al found troublesome reactions in 26.5 per cent of the patients, and 8.7 per cent of injections. Only 4 per cent of the patients, however, requested a return to the intramuscular route of administration.[100]

More recent reports, however, discussing the relative freedom from local reactions with subcutaneous administration, suggest that this may be a matter of technique. Ray and Burch have noted that the absorption of mercurial diuretics is more rapid from muscle, as compared with subcutaneous tissue, and that sloughs may occur in the latter. This may explain why depositing a mercurial diuretic in the subdermal tissues, which are relatively free of fat, may eliminate the formation of fibrous nodules.

ORAL REACTIONS

Gingivitis and stomatitis are common reactions to the newer organic mercurial compounds. Ray and Burch noted stomatitis (in dogs) as more frequent following Thiomerin than Mercuhydrin.[79]

With oral diuretics, Lawrence, Kahn and Riser report gingivitis in three of twenty-four cases on Neohydrin, and two of twenty-four with Cumertilin, although an incidental note is made that the dosage of the latter drug was not sufficient to maintain satisfactory diuresis.[67] In Batterman's series, 9 per cent of the patients taking oral Mercupurin developed gingivitis.[5] In a group of ninety-two cases given Neohydrin, Bradford reports one case of stomatitis.[11]

Stokes, as quoted by DeGraff and Nadler,[24] has pointed out that stomatitis and excessive salivation are not reliably associated with these drugs *per se* because they are dependent rather more on the state of bacterial flora of the mouth than upon oral hygiene. Riser attributes to electrolyte imbalance two cases of stomatitis among 125 patients receiving 4100 injections in twenty-four months.[82] Doherty et al noted that with Neohydrin these symptoms usually ceased to be a problem when oral hygiene was improved or dosage readjusted.[27] Donovan and his associates, in thirty-two cases given Neohydrin, reported one patient with gingivitis and stomatitis which they related to poor oral hygiene.[28]

GASTROINTESTINAL REACTIONS

Gastrointestinal reactions are commonly experienced with the newer mercurial drugs, and again appear to be related to the specific characteristic of each drug, as well as to the route of administration.

Intravenous injection of Salyrgan with theophylline produced cramps in five of 150 patients, while there was no such reaction with either Mercuhydrin or Thiomerin. In one series, intramuscular administration of Thiomerin or Mercuhydrin produced cramps and nausea in about 1 per cent of the subjects. In another series of 140 patients, Thiomerin, injected subcutaneously, was reported to produce five cases of cramps, six of nausea, and three of diarrhea.

Oral diuretic agents are looked upon with considerable favor because of the ease of administration, which may in part offset the minor side effects, which may be further minimized if the drug is taken after meals. Gastrointestinal symptoms may disappear as the same drug is continued, as with Derow's patients who were receiving oral Mercupurin.[25a]

Moyer et al noted gastrointestinal symptoms from Neohydrin, sufficiently severe as to require cessation of the drug in three of twenty-eight patients, but remarked that these had been given large initial doses. They therefore suggest smaller initial doses, with gradual increases to the point of compensation.[76]

Doherty et al encountered minor reactions, such as nausea, vomiting and diarrhea, in only 10 per cent of fifty-eight Grade III and four Grade IV patients who were given Neohydrin for periods as long as fourteen months.[27] In thirty-two patients taking Neohydrin, Donovan et al saw three with gastrointestinal reactions, one with vomiting, one with abdominal pain, and one with diarrhea.[28]

Of twenty patients given Neohydrin, Finch stated that two suffered nausea on the first day, with no recurrence, and one had nausea and diarrhea on the twentieth day of administration.[30] Kaplan et al report no gastrointestinal symptoms in fifteen patients given Neohydrin.[59] Of thirty-three patients taking Neohydrin for up to eleven months, there were two cases of diarrhea and one of vomiting.[68]

Bresnick and Abramson treated fifteen patients with Neohydrin up to eighteen months, with one patient discontinuing the drug because of recurrent nausea and vomiting.[12] Bradford, in ninety-two patients given Neohydrin for up to eighteen months, found no nausea, vomiting or diarrhea sufficient to warrant discontinuation of treatment.[11] In thirty-two patients on Neohydrin for one year, Mauriello and Re report two with severe gastrointestinal reactions.[69] As has been noted, a number of clinicians advise small initial doses of mercurial diuretics, gradually increased, in order to avoid gastrointestinal reactions.

SKIN REACTIONS

The type of epidermal reactions seen following mercurial diuretic therapy commonly includes generalized pruritus or urticaria. More rarely, the patient presents morbilliform or purpuric eruptions, and, most rarely, exfoliative dermatitis.

Although reactions in the skin often occur alone, they may be accompanied or followed by chills, fever, and asthma, and may therefore be warnings of impending systemic or anaphylactoid reactions. Innocuous and reversible as they so often are, their warning cannot casually be ignored. They frequently occur after successive courses of administration, growing more intense each time. They are apparently allergic in nature, and are clearly due to sensitivity or sensitization.

In some patients, such sensitivity must apparently be present to the organic compound, and not to mercury, or perhaps to the mercury in one conjugate and not to mercury in a slightly different conjugate. These patients react epidermally to one mercurial diuretic and not to another. This has been seen in a patient who developed urticaria following Mercupurin, and none with Mercuhydrin.[32] The development of such sensitivity is seen in Reeves' patient, who tolerated eleven successive days of 2 cc. Mercuhydrin injections before developing a temperature rise to 101.6° F. The twelfth injection raised the temperature to 103° F. and the next to 103.8° F. Nevertheless, the patient tolerated Thiomerin, administered four and a half months later.[81] In this patient, sensitivity to the first compound may not have been accompanied by sensitivity to the second. On the other hand, in the time which elapsed between courses of treatment, sensitivity may have been lost, or tolerance acquired. Tournai's patient had received both Salyrgan and Novurit. One day, twenty seconds after the injection of Novurit, he reacted with a papular rash, which developed into a hemorrhagic urticaria of five weeks' duration. Later Novurit injections caused severe urticaria, but Salyrgan was well tolerated.[98]

On the other hand, cross-sensitization is sometimes seen. A patient studied by Fox and his associates[37] responded within ten minutes after an intravenous injection of 0.5 cc of Mercupurin, with labial angioedema, conjunctival injection, a diffuse erythematous eruption, and a temperature

rise to 103° F. Although there was a variation in the degree of reaction, other organic mercurial diuretic compounds caused similar responses. This is not surprising, if we consider the close chemical relationship. To sodium salts of propylcamphorinic acid are attached slightly different mercury compounds, giving us Mercupurin or Mercuzanthin (mercurophyllin), and Thiomerin (mercaptomerin). There are similarities in the structural formulae of Neptal and Salyrgan. By biological responses, it appears that Salyrgan and Mercupurin act similarly in the reactions they cause. In Blackford's case report, both suppository and intravenous Mercupurin caused wheal formation.[9] Similar, but less, response followed Salyrgan administration. Oral Salyrgan-theophylline caused intense urticaria. Here successive treatments may progressively sensitize the patient. We cannot, unfortunately, reverse our time sequence and repeat the experiments with the drugs used in inverse order.

A perfectly typical clinical reaction is that described by Gottlieb.[47] The patient showed no abnormal response to four intramuscular injections of Mercupurin. A fifth, given intravenously, seven days later, caused a temperature of 101.6° F., and a generalized urticaria. Another injection seventeen days later was followed by urticaria and angioedema. Some patients sensitized by injection treatment do not similarly respond to oral administration. Donovan et al note that a patient who could not take parenteral mercurials without skin reactions, tolerated (and without unfavorable response) oral Neohydrin.[28]

The usual type of patch test may be negative, but patch tests applied to abraded skin can be followed shortly by pruritus and generalized urticaria, as in Gottlieb's case.

The reaction by exanthematous eruption and positive test does not necessarily mean permanent sensitivity. Burrows and Stokes describe six patients in whom the use of Neptal caused an exanthematous eruption. In all, patch tests were described as positive. The cessation of Neptal administration led to a reversal of the skin reaction, subsequent patch tests becoming negative. Readministration of Neptal caused no ill effects.[18]

True sensitivity is probably best proven by reverse passive transfer with post-treatment serum. Normal serum and that taken from a patient being treated with the mercurial in question, are both separately injected intradermally into the patient in whom sensitivity is suspected. A positive test to the donor's serum proves the presence both of the antigenic activity of the serum of any patient taking mercurial diuretics, as well as the sensitivity of the recipient. Gelfand demonstrated this in a patient in whom temperature rise could be induced at will after injection of Mercuhydrin.[39] Although intradermal skin tests were negative, the intradermal injection of serum taken from *another* mercurial-treated patient was positive. When mercury administration of the donor had been stopped

for some time, the intradermal test of his serum was negative, as was normal serum.

How common are such reactions? In a series of seventy-four patients given Mercupurin, Finkelstein and Smyth did not observe one case.[32] Bradford noted two cases of maculopapular rashes in ninety-two patients given Neohydrin.[11] In both the rash cleared when the drug was withdrawn. In a series of thirty-two patients studied by Mauriello and Re, Neohydrin given for twelve months resulted in no cases of skin eruptions.[69] However, any eruption occurring in a patient taking a mercurial should be viewed with suspicion as a possible warning of an impending generalized sensitivity.

RENAL EFFECTS

Granted the mode and site of action of the mercurial diuretics, it is noteworthy that the literature makes so little mention of kidney effects. Batterman reports uremia following oral Mercupurin. There was nausea and vomiting, with a rise in nonprotein nitrogen. He feels that Mercupurin should not be used in patients with impaired kidney function.[5] Sprague and Graybiel[93] and also Herrmann and Decherd[55] have reported mild renal irritation, and Derow a relatively severe renal irritation caused by Salyrgan.[25] Mercupurin has also been reported to cause mild irritation.

On the other hand, in post-mortem studies on thirty patients who received Salyrgan for extended periods of time, Tarr and Jacobson found only one with a renal lesion.[96] Reviewing the available evidence, DeGraff and Nadler conclude that the risk of uremia is not great. They remark that a rise in blood urea may occur, but that this is generally interpreted as due to hemoconcentration rather than kidney damage.[24] Doherty et al note that many patients in cardiac failure may exhibit various degrees of renal failure secondary to cardiac decompensation. They suggest caution in the administration of mercurial diuretics if the NPN exceeds 60. They recommend that if the NPN rises higher than the pre-treatment level, the drug be discontinued, or a rest period given.[27]

Batterman, after studying a group of patients who presented an albuminuria before or during mercurial treatment, says that albuminuria does not in itself contraindicate the continued use of mercurial diuretics, since these patients do not develop signs of greater toxicity.[5] Gold concludes that "There is not evident contraindication to doses of the mercurials in patients with congestive failure, regardless of the state of the kidneys."[43] Bruno cites the fact that much evidence is accumulating that patients with renal impairment respond well to the administration of mercurial diuretics.[17] Goldring remarks that there is no reason to believe that the diseased kidney is more vulnerable to the toxic reaction of mercury than is the normal kidney, and that there may be reason that the functionally impaired kidney is *less* likely to injury, since its

inability to concentrate would result in a more dilute solution of mercury in its tubular fluid.[44]

OTHER UNCOMMON REACTIONS

Cardiovascular Effects.—The so-called "cardiovascular reaction" is not common, and especially at normal therapeutic levels. When it occurs, it is probably due to high plasma concentrations following rapid intravenous injection. Serious, although rare, it was at one time thought to be due to direct effects upon the myocardium, and in animals, it is known that large doses of mercurials will cause myocardial reactions. In man, we cannot be certain, because the proper experimental conditions cannot be arranged. Finkelstein and Smyth have taken electrocardiograms before and after intramuscular injections of Mercuhydrin, in 40 patients, and discovered no apparent lasting heart changes.[32] Neohydrin is said to cause no detectable cardiac effects excepting in exceedingly large doses.[51] Thiomerin, a mercaptan compound, is reported as showing no cardiac effects,[2] but because it is retained in the system for long periods of time it tends to produce a higher frequency of other types of toxicity, which more than counteract the absence of cardiac damage following its use.[3,41,42,79]

Bone Marrow Effects.—As rare, but as serious as cardiovascular effects, are those reactions causing bone marrow depression. Such cases as are reported point not only to a true blood dyscrasia, but specific sensitivity. One case report describes Salyrgan-theophylline as producing a profound neutropenia, although another mercurial diuretic agent was well tolerated.[89] Mercuzanthin was held responsible for a bone marrow depression with severe agranulocytosis seen in a patient following ten months of Mercupurin administration.[7] In both cases, recovery followed treatment with BAL.

Here, as with cardiovascular effects, experimental studies cannot be arranged, chiefly because of the rarity of the disorder. Morrison and Greenblatt, in special studies of the long bones of seven patients given Mercuhydrin from six months to four years, found no changes of any type.[74] Long-range studies on many patients would be required to give us any understanding of the type of allergic factors involved.

Systemic Reactions.—For want of a more descriptive term, a special type of reaction, associated with chills and fever, palpitations, tachycardia, arrhythmias, fall in blood pressure, with dizziness and vomiting, has long been known as the "systemic reaction." This may be allergic in nature, suggested by the fact that it most often occurs in patients taking treatment for prolonged periods of time. After such a "sensitizing period," mild reactions occur, and grow more and more severe with each successive injection of the mercurial diuretic involved. In the series of

Gold et al, 209 patients were given subcutaneous Thiomerin. In 16 per cent, reactions occurred for the first time after a considerable period of treatment, and increased in frequency and severity as the injections were continued.[42] The rarity and specificity of such reactions are both illustrated by the studies of Modell et al. In ninety-two patients given 1,729 injections of two mercurial diuretics, only two patients developed unfavorable systemic reactions. In each case, the substitution of another mercurial was well tolerated.[73]

WHEN IS A "REACTION" NOT A REACTION?

A number of reactions frequently attributed in the literature to mercurial diuretics are not truly due to the drug, but, as previously noted, are the results of diuresis causing sodium, potassium or calcium deficiency. Other sequelae which must be discussed include the effects of hemoconcentration, digitalis toxicity related to potassium loss, vitamin deficiencies, and rarely, an attack of gout. As Doherty et al point out, none of this group of reactions should occur, because they are "usually a result of overzealous or enthusiastic treatment, and can be avoided in almost every instance by careful handling of the patient."[27] When the injections are given too frequently, serious dehydration may develop, the patient presenting tachycardia, uremia and shock. These may be present, although some edema remains, despite the increased excretion of water and the chlorides of sodium, potassium and calcium.

Early symptoms of salt depletion are restlessness, abdominal cramps without diarrhea, leg cramps, tachycardia, thirst, nausea, lassitude and fatigue, progressing to stupor and coma. There is no diuretic response to the mercurial diuretic agent injected. The blood presents a high urea content and urea clearance is decreased, as confirmed by laboratory studies. Hemoconcentration may mask the salt depletion. Unless hypertonic saline is ingested, or, in severe cases, injected, the patient dies. With the injection of no more than 2 cc of the diuretic agent once, or at the most twice, weekly, the salt depletion syndrome should not occur.[27,57,58,97]

Hypokalemia may be seen following or accompanying hyponatremia. It can be recognized by the laboratory studies and the electrocardiographic changes. It can be prevented by high potassium intake (orange juice) or potassium salts. With low serum calcium, tetany may be seen.

Excessive diuresis may involve potassium hypersecretion, which occurs when sodium is so greatly depleted that potassium is substituted. However, many observations on increase in potassium excretion give the impression that potassium depletion is much more common than it actually is. Mercurial diuretics specifically inhibit potassium excretion. However, it has been observed that when potassium excretion has been subnormal, the diuresis tends to permit "more efficient utilization of the

capacity to secrete potassium, even though the latter capacity be reduced by the direct action of mercury."[8] The net effect is a more normal rate of potassium excretion.

Hemoconcentration will not only mask the blood level readings of salts, but in itself be the cause of increased blood viscosity and accelerated clotting time. These may directly or indirectly lead to phlebothrombosis, coronary or cerebral artery thrombosis, or pulmonary embolism. Osmotic pressure changes, as well, may cause additional heart strain and result in pulmonary edema. Excessive potassium loss or mobilization of digitalis in edema fluid may cause signs of intoxication, with gastrointestinal symptoms and conduction disturbance signs.

Depending upon the amounts of sodium or chloride ions excreted, varying degrees of alkalosis or acidosis may be present. Electrolyte determination will establish the need for ammonium chloride, hydrochloric acid, or acetazoleamide. As noted above, rarely in gouty patients, diuresis may provoke an attack of podagra, and in those suffering from malnutrition may bring to light pellagra or riboflavin deficiencies.[4,88]

If reactions following mercurial diuretic agents are to be minimized, the drugs should not be administered in the presence of acute glomerulonephritis, and should be used with caution in chronic renal disease. Difficult though it may be to determine whether an azotemia, albuminuria, and hematuria, in the presence of congestive heart failure, is due to primary renal disease or to heart failure, it has been pointed out that a moderate degree of renal damage is not a contraindication for the use of diuretic drugs.

When no response is obtained from a mercurial diuretic, it should be discontinued until the possible electrolyte imbalance is corrected. When a sensitivity reaction to a mercurial develops, another preparation may be cautiously substituted. A minor reaction, such as leg cramps, is not a contraindication, but suggests smaller dosage or less frequent administration.

SUMMARY AND CONCLUSION

Any appraisal of the literature concerned with reports of reactions to mercurial diuretics must take into consideration factors other than the drug itself. To the extent that the drug is involved, one must consider which mercurials have been used, and how, and when. A great number of the fatal reactions occurred early in the history of the mercurial diuretic therapy, and the drugs involved were therefore the original, more toxic compounds, and at that time the chosen method of administration was by vein. The management of the patients was not sound in the light of our present knowledge.

The advent of the newer organic mercurial complexes, with the use of intramuscular, subcutaneous and oral administration, more cautious dosage schedules, and the judicious awareness of the implications of early

minor side reactions, have led to the report of surprisingly few fatal reactions, many fewer than one would expect on the basis of idiosyncrasy to so commonly used a drug. Either such reactions are not being seen, or, if noted, are not being reported. In contrast to the reports of reactions which have been published, Vogl has stated that in thirty years he has not seen a single serious reaction following intramuscular or subcutaneous administration of a mercurial diuretic.[105] Other long experience with large series of cases has been cited, in which no serious reactions to these drugs have been observed. It has previously been stated that in one clinic 13,000 injections of mercurial diuretics have been administered during a four-year period, without any ill effects.[67a]

If this record of safety for these important drugs is to be maintained, how are they to be handled? When the physician is alert to problems of dosage in relation to the patient's age and weight, to water and electrolyte balance, to side effects as evidenced by excessive diuresis, and to the possibility of allergic reactions, then toxic effects due to high level dosage should easily be avoided.

The small group of truly allergic patients can be recognized and treated with the proper precautions. The history will, of course, if directed towards discovering "drug reactors," help uncover those who require special handling. Treatment should always be initiated with a small dose of the magnitude of 0.2-0.5 cc. Skin tests intradermally, of the mercurial, and patch tests, even on abraded skin, are not dependable. The injection of 0.05 cc of serum from a patient taking the mercurial in question (and not sensitive to it) injected intradermally will, as noted above, often result in a wheal, if the recipient is sensitive to the mercurial diuretic. Since normal serum evokes a slight to moderate response, the test must not only be done with good technique, but interpreted qualitatively as well as quantitatively. A positive reaction does not mean that the patient cannot tolerate with safety another mercurial diuretic, especially if the same precautions are followed, both for the proof of sensitivity and the trial of small doses, given cautiously.

In this connection, as has recently been pointed out, "choice of a diuretic agent may be directed to different classes of compounds, as well as to differences within each class. The routes of administration constitute another basis for choice."[41] It would appear from this study that mercurial diuretics are remarkably safe drugs when rightly used. Such use, however, requires a recognition of the fact that the patient who needs them presents a dynamic system involving the interplay of a number of physiologic and pathologic processes, all of which must be taken into account if the maximum safe response is to be obtained. In few other areas of medical science must the physician exercise such nicety of judgment. On the other hand, in few fields of treatment are the results so gratifying.

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SWELLING OF THE INTERPHALANGEAL JOINTS AS A MANIFESTATION OF DRUG ALLERGY

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DRUG hypersensitivity manifested primarily or predominantly on the phalanges, to my knowledge, has not been described in the literature. The following cases observed in military and private practice are reported in order to direct attention to this syndrome, which may occur either alone or in combination with other manifestations of allergic sensitization.

CASE REPORTS

Case 1.—While in the Army during World War II, J. L. W., a colored man, was admitted to my service in the 180th Station Hospital in Oran, North Africa, on June 4, 1943, with a diagnosis of chancroid. He was started on sulfathiazole, 4 grams initially, followed by 1 gram four times daily for five days. On the third day, June 7, after 17 grams of the drug had been taken, the patient felt a tingling sensation in the tips of his fingers. The following morning, the fingers were stiff at the distal and middle interphalangeal joints and very tender over the volar surface of the distal portions. Thinking the symptoms would clear up, the patient did not report them and continued on the medication. His first report of his complaint was at 10:00 a.m. on the fifth day of medication, June 9, when he had taken a total of 22 grams. Examination revealed no rash. The fingers were moderately edematous from the middle interphalangeal joints to the tips. All the fingers except the right fourth and left fifth were exquisitely tender on the volar surface of the terminal portions. Epinephrine borate was given hypodermically at 11:00 a.m., followed by a 3/8 grain capsule of ephedrine sulfate orally. Some relief of the pain was obtained. At 11:15 a.m., a blood count revealed 5.1 million red blood cells with 90 per cent hemoglobin (Talquist), 8,000 white blood cells with a differential count of 81 per cent polymorphonuclear leukocytes, 17 per cent lymphocytes, and 3 per cent monocytes. Free blood sulfathiazole was 3 mgs per cent. Sulfathiazole therapy was discontinued and fluids were forced. In ten hours, all the tenderness in the fingertips was gone, and the edema had completely subsided in forty-eight hours.

Sulfathiazole was restarted forty-eight hours later, 1 gram four times daily to tolerance, in an attempt to reproduce his former reaction. For military reasons, he was discharged three days later, June 16, having taken 12 grams without a recurrence of the reaction.

Case 2.—B. R., a twenty-four-year-old white pattern maker, was treated in 1949 for gonorrhea with 300,000 units of penicillin daily for three days. He was seen in my office on June 19, 1954, because of a urethral discharge of one day's duration. A smear of the discharge revealed the presence of gonococci. He was given 2.4 million units of penicillin (Bicillin®) intramuscularly. Within twenty-four hours the discharge disappeared. Eight days later, on June 29, 1954, marked itchiness of the fingers developed. Two days later, the fingers of both hands became stiff and swollen, and the toes were itchy and swollen. The patient had difficulty in walking

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and could not work because of the inability to use his fingers. Examination showed edema of all the fingers and toes in their entirety. A few urticarial wheals were present on the fingers and a sparse papular eruption on both knees. The remainder of the body, including the toes, was free from any eruption. Epinephrine hydrochloride (1:1000) 0.5 cc by hypodermic injection relieved all the symptoms within a few minutes. He was then given Acthar® Gel (80 units) intramuscularly. The next day he was able to walk. A papular itchy eruption was present on the dorsa of the feet, Achilles tendon area, and both elbows. The first right finger was the only one that remained swollen. A slightly itchy erythematous eruption was evident on the palms. Acthar Gel (60 units) intramuscularly was repeated. By the next day, July 1, 1954, the stiffness and swelling of the fingers and toes had completely disappeared. Hydrocortisone, 20 mg twice daily, replaced the Acthar Gel and was continued for four days. Recovery continued and there was no recurrence of symptoms upon completion of the hydrocortisone therapy.

Case 3.—S.G., a fifty-nine-year-old white tailor, consulted me on May 27, 1954, because of an inability to close his hands and pain in the neck on motion for the past few days. He had had a subtotal thyroidectomy for hyperthyroidism in 1946. In 1945, he suffered from an attack of acute coronary thrombosis. The basal metabolic rate in 1947 was plus 2 per cent. There was no history of allergy.

On examination, there was pain on movement of the head to the left. The hands, including the fingers in their entirety, were edematous and the fingers could not be closed completely. The condition of the fingers suggested an allergic etiology and epinephrine hydrochloride, 0.5 cc of a 1:1000 dilution, therefore was given. The response was dramatic. The fingers could be closed completely after about two to three minutes. Further questioning revealed that since the beginning of April, upon the advice of another physician, the patient had been taking 1-grain thyroid tablets,* four daily, and Hepron.†

Ambodryl® 25 mg three times daily was prescribed. The next day there was a recurrence of the same complaint. However, the hands were only slightly swollen. Intravenous Benadryl® (30 mg) brought no relief. Epinephrine hydrochloride (1:1000) 1.0 cc hypodermically resulted in some relief. He was then given Acthar Gel (80 units) intramuscularly and advised to take hydrocortisone orally, one 20 mg tablet four times daily for the next three days. Thyroid tablets were discontinued. He was seen again on June 9. Some stiffness of the hands was still present upon arising in the morning, which was relieved by soaking in warm water, but there was no swelling. This same day, he developed pain and limitation of motion in the left shoulder. Physical and fluoroscopic examinations were compatible with a diagnosis of an acute calcific subdeltoid bursitis. This was relieved by a local injection of 2 per cent procaine intramuscularly, Acthar Gel, and oral hydrocortisone. By about June 15, the stiffness in the hands was gone. Basal metabolic rate on June 20 was minus 8 per cent. He was asked to take the same thyroid tablets he had taken before. He took one grain twice on June 25. The next day, he awoke with stiffness in the hands. He discontinued the thyroid medication, and the symptoms disappeared in a few days. Upon request, the patient repeated two grains of the drug on July 1 with similar effect.

Which factor in the thyroid preparation was responsible for this reaction could only have been ascertained by further experimentation, to which the patient would not agree.

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*Parke-Davis Emplets, Thyroid "Strong." Each one grain tablet is equivalent to 1½ gr of thyroid U.S.P.

†Hepron (Rossman Laboratories) contains secondary liver fraction 3 gr, ferrous sulfate exsiccated 1½ gr, and vitamins A, B_1, B_2, C and D, calcium pantothenate and niacinamide.

DISCUSSION

These cases resemble a fixed eruption insofar as the signs of allergic sensitivity to a drug repeatedly appears in the same location of the body. The fixed eruptions are thought to be due to sensitization of certain tissues (shock tissues?) of the body without generalized sensitization, or that certain tissues may be more reactive than others even though sensitization is general.[1,2]

In the cases described, there was previous drug contact in Case 2, probably also in Case 1.

Though the drugs were different, they produced the same type of reaction. The interphalangeal joints were apparently the most reactive portion of the body and acted as "shock organs."

In Case 2, there was also a sparse skin eruption present.

I am familiar with the history of two other patients whose dominant complaints were pain, stiffness, and swelling in the fingers after the ingestion of sulfathiazole, but who also had generalized itchy eruptions.

Epinephrine, ephedrine sulfate, antihistamines, and steroids were used in the treatment of these patients. All the patients responded and made a complete recovery.

CONCLUSIONS

Three patients are reported whose allergic sensitization manifested itself solely or predominantly in the phalanges of the hand with or without palmar involvement in two and also in the phalanges of the feet in the third. Sulfathiazole, penicillin, and desiccated thyroid were the sensitizing agents.

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A NEW ANTIHISTAMINE* FOR TREATMENT OF VARIOUS ALLERGIC MANIFESTATIONS

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BROWN[2] has stated that allergy is one of the youngest subdivisions of medicine and has the shortest modern history. This is due, according to this author who has contributed much to the field of allergy, to a non-acceptance of three basic hypotheses: First, that a group of individuals can be affected by everyday substances; second, that the first and subsequent exposures lead to no overt signs or symptoms; and, third, that the specific responses to known sensitizing agents can be induced by nonallergenic or physical agents as well as by emotional and mental states. Wittich[9] stated that no tissue can escape allergic manifestations and that every cell in the body shares in allergic disease, although this might be apparent only as a major cause of difficulty in the chief shock organ affected.

No effort will be made to review all of the therapeutic advances made for the treatment of allergic disturbances. This report is confined to a discussion of a new antihistaminic agent as an adjunct in the treatment of various allergic manifestations.

HISTAMINE-ANTAGONIZING AGENTS

It has been shown that histamine or a histamine-like substance is released in the tissues in allergic reactions which lead to the production of substances acting as histamine antagonists. Sheldon[8] stated that antihistaminics have many pharmacologic properties and because of this they have been recommended in cases of anaphylactic reactions or severe allergic shock, and as a result they have been found effective in such conditions as urticaria, angioneurotic edema and hay fever. All are antianaphylactic and antiallergic. They protect an animal against histamine shock; they are sedative in action, they have atropine-like activity, they have local anesthetic activity and are useful in such procedures as preoperative bronchoscopy. Antihistaminics are also antiemetic, have an effect on the enzyme system and give an antihyaluronidase reaction which makes them efficacious in many cases of contact dermatitis and atopic eczema. Feinberg[4] stated that a very valuable and basic series of compounds in the form of the antihistamines has been added to the physicians' armamentarium in the last few years. They have been shown to be useful in many disease entities and symptoms, being mostly effective in the treatment of some allergic diseases.

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*(1-methyl-4-amino-N'-phenyl-N'-(2'-thenyl)-piperidine tartrate)

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NEW ANTIHISTAMINE—CLEIN

A study was undertaken to evaluate a new antihistamine in the hope that it would be free from some of the undesirable side effects of all other antihistamines. This product (Sandostene*) was found to produce less sedation and drowsiness than other antihistaminics. It was made available in tablets, each containing 25 mg 1-methyl-4-amino-N'-phenyl-N'-(2'-thenyl)-4 amino-piperidine tartrate; syrup, each 4 cc (approximately 1 teaspoonful) containing 12.5 mg of antihistamine and the equivalent in calcium ion content to 1 gm of calcium gluconate; ampuls, each 10 cc containing 50 mg of 1-methyl-4-amino-N'-phenyl-N'-(2'-thenyl)-piperidine tartrate in 10 per cent solution of calcium gluconogalactogluconate.

CHEMISTRY AND PHARMACOLOGY

Sandostene is 1-methyl-4-amino-N'-phenyl-N'-(2'-thenyl)-piperidine tartrate. Rothlin and Cerletti[7] showed that it has a high antihistamine activity in the isolated guinea pig gut.

In comparison with a large series of therapeutically-used antihistaminics, this product occupies an intermediate position between the weakest and strongest. Comparison of its anticholinergic properties with those of atropine on the isolated ileum and seminal vesicle of the guinea pig and on the perfused isolated superior cervical ganglion of the cat showed that weight by weight from 50 to 100 times more Sandostene than atropine was required to antagonize the effect of acetylcholine. Since its therapeutic dose is 50 to 100 times that of atropine, its anticholinergic action must be considered therapeutically significant. Tested on the rabbit cornea, it was found to be equal to procain and 2.2 times less effective than panthesine in its local anesthetic effect. In acute and chronic experiments, it showed low toxicity. These values are significantly higher than those of the average antihistaminics in use today.[6]

THE EFFECT OF CALCIUM ON THE SPECIFIC PROPERTIES OF THE ANTIHISTAMINE

The addition of a calcium salt was not found to alter the antihistaminic action; nor the anticholinergic and local anesthetic effects of the antihistamine. It is interesting to note that the antihistamine appears to counteract some of the undesirable calcium effects, such as cardiac irregularities. The mutual increase of tolerance of calcium and the antihistamine is exhibited also by the fact that larger quantities of the two components can be tolerated in combination than might be expected if a simple addition of the proportionate toxicities of the two substances occurred.

EFFECTS ON PERMEABILITY

One of the therapeutic effects of calcium is manifested in decreasing tissue permeability, a property which is attributed also to the antihistaminic group of agents. Observations have revealed that relatively small doses

*Furnished by Sandoz Pharmaceuticals, San Francisco, California.

(10 mg/kg) of this product plus calcium give complete protection. Calcium alone also exercises some incomplete inhibitory action; the addition of the antihistamine greatly intensifies the effect of calcium.

CLINICAL OBSERVATIONS

A few papers dealing with the clinical properties of the antihistamine alone and in combination with calcium have appeared in the European literature. Huber[5] described the permeability of the barrier between the blood and the aqueous humor of the eye and showed that histamine, acetylcholine and other H-substances are probably among the principal causes of an increase in vascular permeability. The action of calcium, and in part the action of antihistamine, is due to a reduction in the permeability of the vessels.

Bigliardi[1] obtained best results with the drug in the treatment of acute urticaria, acute Quincke's edema, exudative urticarial eczema, drug rashes of the cutaneous vascular reaction type, essential pruritus, allergic rhinitis and in the prevention of allergic intolerance during specific desensitization. Chronic urticaria, pruritus due to eczema and neurodermatitis, as well as bronchial asthma, may not respond so well.

Essellier, Forster and Morandi[3] report their results with the antihistamine and the antihistamine plus calcium in 109 patients in which a good therapeutic effect was obtained for pruritus, urticaria, transfusion reaction.

In our series, 124 patients were treated with the drug alone and in combination with calcium, orally and intravenously, from May through August, which is the pollen grass hay fever season in the Pacific Northwest. These represented pollen hay fever cases with other forms of previous allergy. All patients under six years of age were treated with the syrup of the antihistamine plus calcium, and all patients over six years of age were treated with the tablets. The average dose of the syrup was one teaspoonful three or four times a day. If the patient improved, the dose was reduced to determine the minimum effective dose. If favorable results were not obtained within a few days, the dose was doubled. This same procedure was used in the case of the tablets. The intravenous form of the product plus calcium was used in severe urticaria in combination with angioneurotic edema. The cases treated were as follows: pollen grass hay fever, 76; hay fever plus asthma, 12; eczema, 17; perennial allergic rhinitis, 8; urticaria, 4, and angioneurotic edema with urticaria, 7, making a total of 124 cases.

It was our belief that the use of this drug in the acute persistent pollen hay fever cases would be a critical test of the value of any new drug.

The antihistamine was given to 105 patients whose symptoms were aggravated during the hay fever season. About 50 per cent of this group were old patients who had been thoroughly studied and treated for various forms of allergy and who were doing well until the onset of the grass pollen season. The remainder of the children were new patients

TABLE I.

Indications	No. of Cases	Results				
		Excellent	Good	Fair	None	Side Effects
Hay fever	76	10	22	29	15	2
Eczema	17	2	—	6	9	none
Hay fever and asthma	12	2	7	—	3	none
Perennial allergic rhinitis	8	—	8	—	—	none
Urticaria	4	2	1	—	1	none
Urticaria with angio-neurotic edema	7	5	—	—	2	none
Total	124	21	38	35	30	2

in whom we made the diagnosis of acute pollen hay fever (history, symptoms and positive grass pollen tests). All in this group were given grass pollen antigen. The antihistamine was given only to those patients whose symptoms were not relieved by the grass pollen antigens and other treatment. A group of patients with similar symptoms were used as clinical controls. These were given the usual hay fever treatment including antigen, but without the antihistamine.

METHOD AND RESULTS OF TREATMENT

It has been our experience and that of other observers, that the effectiveness of antihistaminics can usually be determined within the first week of treatment. We found this to be true also of this product. If the patient was not relieved the first week, the dose was then doubled in the hope of relieving the symptoms. Generally, if the patient was not relieved by the average dose of one teaspoonful of the product in combination with calcium three times a day, the larger doses were ineffective also. Those who were administered tablets received from two to four a day depending upon the age and severity of the symptoms. Those patients who were not relieved had two full weeks of treatment; one week the average dose was given, followed by one week of rest, and the third week the dose was doubled.

INTRAVENOUS SANDOSTENE PLUS CALCIUM

Seven cases in this series were given intravenous injections of Sandostene plus calcium in doses of 10 cc for the treatment of angioneurotic edema associated with urticaria. Four cases received 10 cc intravenously given slowly, with excellent results, and with no recurrence of symptoms. One case required a second injection twelve hours later. Two cases were given 10 cc intravenously and did not respond and no further injections were given. It is possible that a second and perhaps even a third injection of 10 cc might have produced the desired results.

Table I.—Eighty per cent of the pollen hay fever cases obtained relief in some degree from the use of the antihistamine alone and in combination with calcium. Forty-two per cent, or thirty-two cases, obtained good or excellent results and twenty-nine cases obtained fair results.

In seventeen cases of eczema (seven under one year of age, six under

TABLE II. AGE DISTRIBUTION IN ACUTE POLLEN HAY FEVER CASES

No. of Cases	To 1 yr.	1-2	2-3	3-4	4-5	5-6	6-10	10-15	15-20
76	6	7	2	5	5	8	19	10	14

two, three under three and one ten years of age), nine were not helped and eight were given moderate relief. Of these eight cases, two infants who had an exacerbation of rash and acute hay fever were greatly relieved.

The children with hay fever and asthma were those who had the most distressing symptoms and included one patient six months of age, two two years of age, four three years, two five years and three ten years of age. Of this group, nine cases obtained good results and three were not helped.

There were eight cases of perennial allergic rhinitis, four of whom had exacerbations due to hay fever. All in this group obtained good results.

Of four cases of urticaria, three were given considerable relief and one case due to a sulfa sensitivity did not respond. Seven cases with angioneurotic edema and urticaria were given intravenous injections of the antihistamine-calcium compound. Five cases obtained excellent results and two did not respond.

Table II.—Twenty-five children from one to five years of age with acute pollen hay fever were in this class. The best results were obtained in this younger age group. These results might be due to the combination of the combined form with calcium, whereas the school age group received antihistaminic tablets alone.

DISCUSSION

All patients treated were those who present themselves in the everyday practice of pediatrics. Most cases were seen in private pediatric practice and others were seen in the pediatric and allergy clinics of the King County Hospital. Our investigation of this new antihistaminic shows that it is effective and it appears to be more advantageous than other antihistamines because of the almost complete lack of side effects. There were only two cases with toxic manifestations of minor significance. One was a boy of ten years of age with pollen hay fever who became nauseated with the tablets and was unable to continue. The second case was a boy of four years of age with pollen hay fever who became cranky each time treatment was reinstituted. Our best results were obtained in the smaller children who did not mind taking the drug. The syrup plus calcium was either given alone or mixed with syrupy fruit juices. Those who obtained most relief were in the group whose symptoms were due primarily to inhalant factors rather than foods. There were no cases of drowsiness and we were particularly impressed with the lack of side effects, especially

in the younger children. Although this antihistaminic, which appears to be more effective than others, is a valuable adjunct in the treatment of various allergic manifestations, specific allergic management is still primary and important in the control of allergic disease.

The availability of this new antihistamine in tablet form, in syrup and ampuls containing the product plus calcium, makes it possible to choose a form most suitable for each patient. The addition of calcium in combination with the antihistamine is an added therapeutic advantage.

SUMMARY

1. Sandostene has a low toxicity and is an effective antihistaminic.

2. It is effective in a high percentage of cases especially in the younger age group in various allergic disorders.

3. Its combination with calcium in syrup and in ampuls results in a potentiation of effect on cellular and vascular permeability.

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NEW PARKE, DAVIS PUBLICATION TO GIVE PHYSICIANS UP-TO-THE-MINUTE POLIO TRENDS AND DEVELOPMENTS

Parke, Davis & Company, producer of poliomyelitis vaccine, has plans for a new medical publication—the first of its kind—giving the latest information on the incidence and distribution of poliomyelitis in major population centers throughout the United States. This report, called "Polio Patterns," will be mailed regularly to physicians.

According to Harry J. Loynd, president, the information in "Polio Patterns" will cover such facts as epidemic, regional, seasonal, and population patterns in the incidence of poliomyelitis. In addition, Mr. Loynd said "Polio Patterns also will report any important new information that may be available about clinical and research developments, prophylaxis or treatment of poliomyelitis."

The data in the new publication will be based on information gathered from official sources, in co-operation with the National Foundation for Infantile Paralysis.

THE INCIDENCE OF ALLERGIC REACTIONS TO PENICILLIN IN INFANTS AND CHILDREN

Further Evidence Collected during the Course of Penicillin Prophylaxis

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NEWSPAPER and magazine reports on the increasing frequency of reactions from penicillin have alarmed so many patients that the physician often is confronted with a marked resistance by patients to the use of penicillin. The purpose of this article is twofold: (1) to review the literature on the question of anaphylactic reactions from penicillin, and (2) to report on our experience with oral penicillin in 402 infants and children seen in private practice with the symptoms and signs of an upper respiratory infection.

As to incidence of reactions to penicillin of any type, most reactions fortunately are of a minor character; of these, Brown[6] reported an incidence of 5 to 10 per cent, Smith and Walker[36] of 10 to 15 per cent, but Levin and Moss[25] only 1.3 per cent in 224 children. In the same year (1951), during a search of the literature on the occasion of a report of two cases of a serum-sickness-like syndrome from penicillin in children (Lapin[23]), this author found no reports of severe anaphylactic reactions in children. For 1952 only two reports (Yoder,[44] Harpman[18]) of anaphylactic shock in a child could be found. In 1952 (Editorial[12]) and again in 1953 (Boger[3]), panels of allergists reported a rapid increase of severe immediate reactions of the anaphylactic type, in patients of all ages, stigmatized by a past or family history of "atopic" allergy. The need for caution has been further emphasized by a report of the Council on Pharmacy and Chemistry[10] and one in 1954 from the New York City Dept. of Health (Jacobziner[20]).

As to the most recent data, Table I lists the fatal and near fatal immediate, so-called anaphylactic, reactions from penicillin reported from January 1953, to date (December, 1954) in patients of all ages.

A discussion of this cursory but probably fairly complete review of the so-called severe anaphylactic reactions due to penicillin must start with thanks to Dr. Henry Welch, Director of the Division of Antibiotics in the Food and Drug Administration, whose painstaking analysis of many hospital records uncovered so many cases that would probably not have been reported. He has been kind enough to analyze his cases for me by age groups, and the results are incorporated in both Tables I and II. Every effort has been made to avoid duplication. It does seem probable that there are many unreported reactions. One hundred forty-nine cases are recorded, 136 in adults, of which sixty-one were fatal and seventy-five near fatal, and thirteen in children (under thirteen years of age), of

TABLE I. FATAL AND NEAR FATAL IMMEDIATE, "ANAPHYLACTIC" REACTIONS FROM PENICILLIN

Reported during 1953 and 1954 in Patients of All Ages

Author	No. Cases	Route of Administration	Type of Penicillin	Adults		Children	
				Fatal	Non-Fatal	Fatal	Non-Fatal
Welch[43]	25	I.M.	Neo-Penil®	5	15	2	3
	57	I.M.	Procaine and O	18	32	3	4
	1	I.M.	Neo-Penil	1	0	0	0
	1	Oral	Bicillin®	1	0	0	0
Fein[14]	1	I.M.	Neo-Penil	0	1	0	0
Pick[32]	1	I.M.	Neo-Penil	1	0	0	0
Stormont[10]	14	I.M.	Neo-Penil	11	3	0	0
Collins-Williams[9]	2	I.M.	Not known	2	0	0	0
Feinberg[15]	8	1 inhalation plus I.M.	1-Procaine oil Procaine 1-Na-G	4	4	0	0
Siegel[35]	3	I.M.	Procaine	1	2	0	0
Rosenthal[33]	8	I.M.	Procaine and O	7	0	1	0
Bell[1]	1	I.M.	Procaine G	1	0	0	0
Chapman[7]	1	I.M.	Procaine G	0	1	0	0
Blanton[2]	1	Oral plus Aerosol	Procaine	0	1	0	0
Christenson[8]	1	I.M.	Procaine	1	0	0	0
Mignault[28]	1	I.M.	Procaine	1	0	0	0
Weiss[42]	1	Instillation Sinus	Crystalline	0	1	0	0
Mayer[27]	6	I.M.	Procaine	1	5	0	0
Sokval[37]	1	I.M.	Procaine	1	0	0	0
Kern[22]	3	I.M.	1-Crystalline G 2-not known	2	1	0	0
Sterling[38]	3	I.M.	Procaine or G	0	3	0	0
Nikishin[31]	1	I.M.	Procaine G	0	1	0	0
Nemser[29]	1	I.M.	Procaine G	0	1	0	0
Ruskin[34]	1	Topical	G	0	1	0	0
Fisher[16]	1	I.M.	Aqueous	1	0	0	0
Brainerd[5]	1	I.M.	O	0	1	0	0
Farber[13]	4	I.M.	Not known	2	2	0	0
Totals	149			61	75	6	7

which six were fatal and seven nonfatal. Of these 149 cases, forty-two are from Neo-Penil® (twenty-six reported by Welch, fourteen by the Council, one by Fein and one by Pick) which may be discounted, because it is now conceded that Neo-Penil may have serious toxic side effects. There remain serious immediate reactions (apart from the serious exfoliative dermatitis, Shwartzman reaction and purpura hemorrhagica reactions which are not listed) to the conventional forms of penicillin in 107 cases, namely ninety-nine adults with forty-three fatalities and fifty-six near fatalities, and only eight children with four fatalities and four near fatalities. The age distribution of the reactions in children is given in Table II. Our analysis shows (if we exclude Neo-Penil) first, that this type of reaction fortunately is still rare in children under thirteen years, and second, that none has been reported with oral penicillin in children.

It seems quite clear from these figures that pediatricians can reassure parents that the incidence of severe reactions from penicillin by any route in children is much lower than in adults. None have been reported with oral penicillin. Whether other types of reactions to penicillin are common in this age group among children is a question which presently will be discussed.

The author's interest in the use of oral penicillin dates back to his

TABLE II. AGE DISTRIBUTION OF CHILDREN REPORTED WITH FATAL OR NEAR FATAL IMMEDIATE REACTIONS (ALL FROM INTRAMUSCULAR INJECTIONS) OF PENICILLIN OR NEO-PENIL

Author	Product	Age in Years								
		0-1	1-2	2-3	3-4	5-6	8	10	11	12
Welch	Penicillin	1	0	0	1	1	0	2	1	1
Welch	Neo-Penil	3	0	0	0	0	1	0	0	1
Rosenthal	Penicillin	0	1	0	0	0	0	0	0	0

study on the prophylaxis of upper respiratory infections in children treated with oral penicillin (Lapin[24]). This study has been extended to the prophylaxis of infection after tonsillectomy and other surgical procedures, rheumatic fever and acute hemorrhagic nephritis. Detailed results will be reported at a later opportunity. During this work, the difficulty of making an exact etiologic diagnosis at the first or even later visits became painfully evident. The exudate of acute follicular tonsillitis is usually missed if the child is seen in the first twenty-four hours; and judgment of viral or streptococcal etiology is much more difficult than might be supposed. In fact, in everyday pediatric practice an exact etiologic diagnosis of trivial upper respiratory infections is often impossible or evidently impractical. Furthermore, if the object is to avoid the complications of infections by penicillin-sensitive organisms, such as cervical adenitis, otitis media, rheumatic fever and acute glomerular nephritis, delay in the institution of therapy would defeat this purpose. For this reason, it seemed interesting to study the effect of oral penicillin given as a routine prophylactic measure to all infants and children who presented symptoms and signs of an upper respiratory infection on the first visit.

Four hundred and two children, from three months to ten years of age, all white (211 male, 191 female), were treated in private practice by oral penicillin during the last two years. This comprises only those whose course could be followed with some confidence. They were seen after a period of fever ranging from a few hours to three days, with symptoms of an upper respiratory infection, and physical signs pointing to a diagnosis of nasopharyngitis, acute follicular tonsillitis, cervical adenitis, mild otitis, influenza, measles or undifferentiated upper respiratory infections. Oral penicillin was not used in several groups: (a) in infants under three months of age, in whom the frequency of staphylococcic infection was so marked that other therapy seemed advisable; (b) in children over ten years of age, because of the expense of the large doses of oral penicillin required to produce adequate levels; (c) in infants and children with a definite history of penicillin sensitivity; (d) in cases with vomiting and diarrheal infections; and (e) in infections seemingly severe at the first examination, such as large cervical adenitis, peritonsillar

abscess, severe otitis media and pneumonia, because experience had demonstrated the advantage of high levels attainable only by intramuscular injection.

Oral penicillin seemed, *a priori,* to have at least three advantages over intramuscular penicillin: (a) psychologic trauma of frequent injections could be avoided; (b) treatment could be continued for as long as desired, often until the child was afebrile for a week, which would have been very difficult with the intramuscular injections; (c) likelihood that the dangerous anaphylactic and exfoliative dermatitis type of reactions to penicillin could be held to a minimum.

The dosage selected for routine administration was 400,000 units of potassium penicillin G tablets at the first dose and then 200,000 every four hours. The soluble variety was prescribed for infants and children under three years of age, and the buffered type for those over three years of age. The dosage was mixed with milk or other foods, and no effort was made to give the dose on an empty stomach. While this dose is higher than usually recommended it has the advantage of giving a higher, longer sustained peak level without the necessity for insisting on administration before meals.

It seems fairly reasonable from a review of the literature (Boger,[4] Flippin,[17] and Huang[19]) to expect that the administration of 400,000 units of potassium penicillin G tablets in the first dose, followed by 200,000 every 4 hours, soluble for those under three, and buffered for those over three, should result in satisfactory penicillin concentrations over most of the 24 hour period.

If the clinical response after forty-eight to seventy-two hours of therapy was not good, re-examination and, where necessary, urinalysis, a complete blood count, and a culture of the throat were done, and any organism recovered was subjected to studies for sensitivity to the various antibiotics. The clinical impression of the prophylactic usefulness of oral penicillin in such a mixed group of upper respiratory diseases was strikingly good. In this group of 402, clinical results were poor in only twelve cases, namely, in four cases of atypical "virus" pneumonia, one case of staphylococcic pneumonia sensitive only to Terramycin® and Chloromycetin,® two cases of otitis media and mastoiditis due to a penicillin insensitive staphylococcus, four cases of infectious mononucleosis, and one case proven to be *Aerobacter aerogenes* septicemia. Of these 402 children, three had a generalized erythema which proved to be roseola (exanthema subitum), two had a rash, urticarial in nature, which could reasonably be attributed to penicillin sensitivity, and six showed slight looseness of the stools, perhaps due to penicillin. No major reactions were experienced.

The author fully recognizes that probably a good number of the children were not suffering from diseases due to penicillin-sensitive organisms. Thus, a large group in March, 1952, were likely due to

influenza infections prevalent at that time. Another large group in early 1954 were unquestionably measles; scattered cases of roseola were quite frequent in the younger age group, and undifferentiated upper respiratory infections probably of viral etiology were also frequent. Most certainly, the use of penicillin does not absolve the physician from the necessity of attempting to make an exact etiologic diagnosis or of good general management. He does, however, suggest that the routine administration of penicillin in this large undifferentiated group of upper respiratory syndromes was responsible for the virtual absence of complications, such as severe cervical adenitis, severe otitis media and mastoiditis, secondary bronchopneumonia, rheumatic fever (Wanamaker[39] and Massell[26]), acute pyelonephritis and acute hemorrhagic nephritis (Neter[30]). Penicillin obviously will be of great usefulness if a streptococcus or a pneumococcus is involved. But also important is the fact that the complications resulting when the initiating organism is a virus, such as measles or influenza, are usually due to a penicillin-sensitive organism and can thus be prevented. This has been already demonstrated in measles by Karelitz.[21] Further studies will be needed in order definitely to settle this question.

We are fully aware that opinion on this point is not unanimous. Thus, a recent report (Cronk[11]) of the effect of oral penicillin G in the treatment of nonspecific upper respiratory infections in Syracuse University students shows no statistical benefit from the use of oral penicillin with aspirin and phenyltoloxamine dihydrogen citrate as compared with those treated with aspirin or phenyltoloxamine dihydrogen citrate alone. There are no blood levels given to show that the absorption of the oral penicillin was not hampered by the simultaneous use of the two other chemical compounds. In addition, the age group treated is well known to possess a far higher resistance to the complications of upper respiratory infections than the infants and children who are the subject of the present report.

It is also important to point out the theoretical objection of many allergists that these children are potentially becoming sensitized to penicillin and may have reactions in adult life. Our answer must be that we have the choice between the statistically rare possibility of producing sensitization to penicillin and the statistically frequent occurrence of severe complications such as otitis, mastoiditis, rheumatic fever and glomerulonephritis in the untreated upper respiratory infections of childhood.

As has already been noted, twelve cases (3 per cent) needed further workup because the diagnosis did not become self evident within forty-eight to seventy-two hours. Of these only 4 were due to penicillin-insensitive bacteria as contrasted to 8 of probable virus etiology. This sounds like an amazingly low percentage of infection due to penicillin-insensitive organisms, but it must be remembered that these were all private unselected cases. Figures taken from hospital records refer to a selected population, which give a far higher percentage of insensitive

organisms than in general practice (Weil[40,41]). Certainly, lack of clinical response should lead to further workup, including throat cultures and testing for antibiotic sensitivity.

Recommendations are made that when intramuscular injections are considered desirable for a severe infection, injections be given in the arm, with epinephrine and injectable antihistaminic and a tourniquet instantly available, and only after a careful history gives no evidence of previous accelerated and, above all, immediate reaction to penicillin.

CONCLUSIONS

1. A survey of the recent literature on fatal and near fatal anaphylactic reactions to penicillin has been made. The conclusion can be drawn that reactions to intramuscular injections, while increasing in frequency in adults, are still rare in pediatrics. None has ever been reported due to oral penicillin in children.

2. Four hundred and two children from three months to ten years of age seen in private practice with initial symptoms and signs of an upper respiratory infection, routinely were given oral potassium penicillin G tablets. The protective effect of avoidance of complications was achieved at the price of only 0.5 per cent of mild urticarial reactions. There were no major reactions. This further strengthens the conclusion that reactions from penicillin are much less frequent and less dangerous in children than in adults. The suggestion is made that oral penicillin be used routinely in an effort to avoid the complications of upper respiratory infections in infancy and childhood.

ADDENDUM

Recently G. H. Stollerman (Bull. New York Acad. Med., 31:165, 1955) reported a very low percentage of reactions to penicillin in children and adolescents in a large series.

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ANAPHYLACTOGENIC PROPERTIES OF PIPERAZINE CITRATE

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SYRUP of piperazine citrate* (Antepar®) has been used extensively and has demonstrated its therapeutic value against *Enterobius (Oxyuris) vermicularis* and *Ascaris lumbricoides* infections.[1,2,3,7]

Cases of what appeared to be allergic dermal reactions from the use of this substance were reported to us. In an analysis of twenty-seven such cases, eight had insufficient data, eleven manifested symptoms which appeared to be unrelated to the drug, and eight appeared to have had a serum sickness-like reaction.

Serum sickness-like reactions do not usually result from the use of a particular drug. They may be accounted for by the concurrent invasion of antigenic substances other than the drug used, a common occurrence during childhood.

In view of the possibility that piperazine citrate might be an allergen, it was subjected to investigation in the guinea pig in an attempt to determine whether it was anaphylactogenic.

MATERIALS AND METHODS

The classic anaphylaxis test was employed to determine the anaphylactogenicity of piperazine citrate. Guinea pigs weighing 250 to 350 g were used in these experiments.

The materials used were syrup of piperazine citrate containing the equivalent of 100 mg of piperazine hexahydrate per cc and an aqueous solution of piperazine citrate of the same concentration.

In certain experiments Freund's Adjuvant[5,6] was mixed with an equal volume of the drug.

TOXICITY STUDIES

In order to determine the dosage that was nontoxic for guinea pigs, for a proper appraisal of hypersensitivity as differentiated from toxicity, a series of animals was tested.

Preliminary experiments disclosed that doses of 5.0 cc of the syrup given intraperitoneally were primarily toxic. The animals promptly succumbed in a tetanic convulsive seizure. The lungs were markedly hemorrhagic at necropsy.

Doses of 1.0 cc intraperitoneally were well tolerated.

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*Kindly supplied by Burroughs Wellcome & Co. (USA) Inc., Tuckahoe, N. Y.

Table I lists a series of animals tested by the intravenous route to determine the optimum nontoxic intravenous dose for shock injection. It will be noted that 0.1 cc of syrup of piperazine citrate given intravenously to thirty-five animals was universally tolerated. When 0.2 cc was given to seventeen animals, there was evidence of primary toxicity in 6 per cent of the animals; and when 0.3 cc was injected into thirty-three animals, there was profound toxicity in 91 per cent of the animals, indicating an MLD 50 of 87 mg/kg.

It was decided therefore that 0.1 cc (10 mg) used intravenously would be the ideal nontoxic dose for testing allergenicity in guinea pigs weighing approximately 350 gm.

TABLE I. TOXICITY TESTS WITH SYRUP OF PIPERAZINE CITRATE

Number of Animals	Primary Injection	Result	Toxicity Per Cent
35	0.1 cc I.V. (10 mg)	34—No effect 1—Slightly restless	0%
17	0.2 cc I.V. (20 mg)	15—No effect 1—Restless 1—Convulsions, recovery	6%
33	0.3 cc I.V. (30 mg)	18—Death 12—Convulsions, recovery 3—Irritable, recovery	91%*

*Critical point of toxicity for guinea pigs weighing approximately 350 gm.

EXPERIMENTS ON HYPERSENSITIVITY

Thirty-four animals were given four sensitizing doses each of 0.5 to 1.0 cc of syrup of piperazine citrate over a period of nine days. These injections were given intraperitoneally in certain instances and subcutaneously in others. Twenty-one days later all these animals were challenged with 0.1 cc of the same substance intravenously. There was no evidence of sensitization noted.

In order to fulfill the criteria necessary to establish sensitization with drugs,[4] which is at best difficult to determine in animals, thirty-seven guinea pigs were subjected to six daily preparatory intracutaneous injections of syrup of piperazine citrate of 0.2 cc each. After a rest period of a week, a second series of similar injections for six days was instituted.**

Sixteen days following the last preparatory injection, twenty-two animals were each given an intravenous injection (0.1 cc) of either the syrup or the aqueous solution of piperazine citrate. In no instance was there any evidence of sensitization established.

In another series, fifteen albino guinea pigs, similarly sensitized, were

**This series of sensitizing doses has been recommended by Chase as an optimum dosage for sensitization with drugs. This schedule corresponds to the therapeutic regimen with piperazine citrate. The recommended therapeutic schedule is treatment for seven days, a lapse of one week, and a resumption of therapy for a subsequent week.

TABLE II.

Number of Animals	Sensitization with Syrup of Piperazine Citrate			Interval	Shock Dose	Result
	First Series	Interval	Second Series			
22	0.2 cc intracut. daily for 6 days	1 week	0.2 cc intracut. daily for 6 days	16 days	0.1 cc I.V. piperazine citrate or syrup of piperazine citrate	0
15	0.2 cc intracut. daily for 6 days	1 week	0.2 cc intracut. daily for 6 days	16 days	0.02 cc intracut. skin test. Observed for immediate and 48 hr. delayed response.	0

TABLE III.

Number of Animals	Sensitization	Challenging Dose 20 Days Later	Result	Second Challenging Dose 22 Days after Sensitization	Result
7	Syrup of piperazine citrate with Freund's adjuvant 1 cc subcut.	Piperazine citrate 0.02 cc intracut. Immediate and 48 hr. observation	0	Piperazine citrate 0.1 cc I.V.	0
13	Syrup of piperazine citrate with Freund's adjuvant 1 cc subcut.	—	—	Piperazine citrate 0.1 cc I.V.	0

challenged intracutaneously sixteen days later with an aqueous solution of piperazine citrate. They were observed for immediate reactions and for a forty-eight hour delayed response. In neither period was there any evidence of sensitivity (Table II).

In a final series of experiments, there were twenty animals sensitized subcutaneously with a mixture of syrup of piperazine citrate and Freund's Adjuvant. Twenty days later, seven of the animals were tested intracutaneously with piperazine citrate solution. They were observed for immediate and forty-eight hour delayed reactions. In no instance was there a dermal reaction. On the twenty-second day the twenty animals were each given an intravenous injection of piperazine citrate solution. No reactions were observed (Table III.)

COMMENT

The hypersensitivity phenomena sought were scratching, irritability, dyspnea, convulsions, collapse or death with typical ballooning of the lungs after the intravenous shock injections. With the dermal test injections, evidence of immediate anaphylactic skin reactions or delayed reactions forty-eight hours later were sought. In none of this relatively large number of experimental animals were any generalized or dermal reactions noted.

Within the limits of our experiments, which satisfy the criteria laid down for the demonstration of allergenicity to drugs, there was no evidence of allergenic properties demonstrable in the drug under investigation.

Whether piperazine citrate will prove to be allergenic for the human subject is doubtful because of the signal absence of sensitizing properties when tested in the guinea pig.

The factors that further militate against the allergenic potentialities of this drug are that it is prescribed orally in a syrup form for a limited time and is not given by injection. True sensitization to drugs results usually from excessive and repeated use over a period of years.

Relative to the instances of hives attributed to the use of this drug, it should be borne in mind that urticaria is frequently encountered during childhood. Such manifestations occur sporadically from many antigenic and nonspecific causes and cannot therefore be readily labeled.

CONCLUSIONS

Insofar as no authenticated case of allergy to syrup of piperazine citrate (Antepar®) has been presented heretofore in the literature and this drug has been shown to be nonanaphylactogenic in the lower animal, it should be regarded as a nonallergenic drug.

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MEDICAL STATISTICS

Writing in the *American Journal of Obstetrics and Gynecology* (69:372, 1955) in an article entitled "Therapy for Intellectual Obesity," I. D. J. Bross deals with the element of chance in any clinical experiment, a factor far too often overlooked. He says that if twenty pennies are shaken in a box and the number of heads that come up are recorded, and the experiment is performed about 100 times, it will be noted that in most trials approximately ten heads will appear, but there will be some instances where fewer or more than ten will appear. This is known as a sampling variation. If the twenty pennies represent twenty patients suffering from a disease ordinarily causing death in 50 per cent of the cases, and if you use a new treatment method and find that out of twenty patients only seven die, you should not be too hasty to proclaim the value of the new therapy, for the sample variation alone could account for these results. If there were fewer than five deaths on one hand or more than fifteen on the other, you might look for an explanation other than the sampling variation. This is the "5 per cent level" commonly used in medicine.

EOSINOPHILIA IN CHILDREN

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THE FINDING of increased numbers of eosinophils in the circulating blood of children is not unusual, and many times it is unexplainable. Its significance is not entirely understood, but in general eosinophilia seems to be associated with detoxification and the disintegration of protein as well as its removal. Eosinophils have some of the powers of neutrophils so far as phagocytosis is concerned and they sometimes seem to replace them in this respect.

The known causes of eosinophilia are listed by Wintrobe[6] as: (1) allergic disorders; (2) some skin disorders; (3) parasitic infestations, especially those which invade tissues; (4) infections such as scarlet fever, chorea and erythema multiforme; (5) disease of the hemopoietic system, such as leukemia, Hodgkin's disease, erythremia, pernicious anemia, and after removal of the spleen; (6) following irradiation; (7) miscellaneous disorders, such as periarteritis nodosum and some ovarian and bone tumors; (8) tropical eosinophilia; and (9) as a familial anomaly.

Nelson[4] states that the normal percentage of eosinophils found in the blood is 3 at birth, 5 at two days of age, 3 until the end of the first year and 2 until the age of twelve years. Kolmer and Boerner[3] give the normal range as from 2 to 5 per cent for all ages from birth to fifteen years.

The author decided to review all the differential blood counts done in the office of his pediatric practice, with special attention to the percentage of eosinophils found. A total of 1107 differential blood counts were reviewed, as well as the records of the individual patients on whom they had been done. These counts had been done during the past nine years on 861 patients ranging in age from seven months to fifteen years. There were 429 males and 432 females in the series. The reasons for doing the counts varied. Patients who had undergone an allergic workup had a differential count done as a matter of routine, and it is the custom in this office to urge a complete physical and laboratory examination at intervals to help determine the general state of the child's health. Many other counts were done to assist in the diagnosis of some specific complaint and these were all included in this study. In each instance at least 100 white cells were counted and all were done by the author.

The average percentage of eosinophils found in the 1107 counts was 4.02. No eosinophils were found in 131 of the counts and the highest percentage found was forty-three in a case of Loeffler's syndrome. Since eosinophilia is generally known to be associated with allergy, those patients on whom a diagnosis of allergy was made are considered separately.

NON-ALLERGIC GROUP

In this group were placed the counts of all patients on whom a diagnosis of allergy was not made at any time. These numbered 674, on whom 841 differential counts were done. The average number of eosinophils found per 100 white blood cells was 3.2. This was well within the accepted range of normal, but there were 145 or 17 per cent of this group of counts that showed an eosinophilia of 6 per cent or more. These were unexplainable.

There seems to be a prevailing opinion that all parasitic infestations show an increase in the numbers of eosinophils found in the circulating blood. Holt and McIntosh,[2] however, are of the opinion that this is not always so. They state that eosinophilia can occur with any of these infestations, especially early in the course, but it is not found as a rule except in trichinosis. There were no known cases of trichinosis in this series. There were three cases of ascariasis and four of oxyuriasis in the series but none showed an increase in the eosinophilia count. Since stool examinations and anal swabs were not carried out routinely, some cases were probably not recognized. Intestinal parasites are not common in this area, although pinworms and roundworms are not unusual. No known cases of visceral larva migrans were encountered in the series.

The other known causes of eosinophilia, with the exception of the allergic syndromes and perhaps the familial anomaly, were not present in the series of cases studied. There were three instances in which siblings had an eosinophilia but the findings were not constant, and it was not thought that they represented a familial anomaly. At this time there is no known explanation for the rather high incidence of eosinophilia found in this group of nonallergic patients. It might be suggested that these patients had an eosinophilia because of some subclinical or as yet unrecognized allergic syndrome.

ALLERGIC GROUP

There were 187 patients, 116 males and seventy-one females, who at some time during the nine years of this study had had a diagnosis of some type of allergic syndrome. These patients represent 21.7 per cent of the total under consideration. This high percentage probably reflects the author's interest in pediatric allergy as well as the fact that all allergic patients seen during the period are included. The allergic patients are tabulated below. The number of counts and the percentage of eosinophils in each syndrome is shown.

Diagnosis	Cases	Counts	Per Cent
Asthma	54	59	9
Hay fever	62	102	6.1
Perennial rhinitis	25	44	4.7
Atopic eczema	13	15	5.7
Allergic cough	10	13	7.7
Urticaria	9	9	6.1
Gastrointestinal allergy	8	8	6.8
Loeffler's syndrome	3	6	12.0
Migraine	3	5	4.5

The average percentage of eosinophils for all the counts done on allergic patients was 6.9 and reflects the expected eosinophilia to be found in allergic patients.

Although many of the allergic patients suffered from more than one allergic syndrome at the same or different times during the period of study, each patient is listed only once under the syndrome which was considered to be the most prominent in that patient.

Eosinophilia is characteristic of allergic reactions but its relation to hypersensitization is not known. In allergy, eosinophils are found to be circulating in the blood and present particularly in the tissues that are reacting. When repeated counts were done on the same patient at varying times, the percentage of eosinophils found was never constant and there seemed to be little correlation between the activity of the allergy and the degree of eosinophilia. Feinberg[1] states that eosinophilia is not an index of the allergic constitution but rather of the active disease; however, Von Niekerk and Van Leeuwen[5] found that patients removed from contact with the offending allergen showed no significant change in the eosinophil count during a period of four to 100 days. The degree of allergic activity is sometimes very difficult to establish, and the problem is further complicated by the fact that seldom is allergic activity brought under complete control.

The presence of an otherwise unexplained eosinophilia should arouse suspicion that the child is suffering from some form of allergy, but its mere existence does not mean that a definite diagnosis can be made without a positive history or additional findings. As has been shown, eosinophilia occurs sporadically in children thought to be entirely well so far as our present state of knowledge is concerned.

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THE USE OF A DOUBLE ANTIHISTAMINE IN THE TREATMENT OF ALLERGIES

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THE value of antihistaminic drugs in the symptomatic treatment of various allergies has been consistently and conclusively proved in hundreds of clinical studies. These drugs have been used with particular success to mitigate urticaria, angioneurotic edema, allergic-rhinitis and some forms of atopic dermatitis. However, findings indicate that the drug with the most powerful and most prolonged therapeutic action will often induce the greatest incidence of side effects.

Loveless and Dworin,[3] in a comprehensive review of clinical research in antihistamine therapy, showed that of 13,190 patients treated for various allergic disorders 66 per cent reported relief. On the other hand, in over 5,000 of these patients, these investigators discovered a range of untoward reactions varying from 13 per cent with a comparatively ineffective antihistamine to 61 per cent with a more potent drug.

The problem of effective antihistamine therapy is further complicated by the wide variation in individual response. Some patients will in time develop tolerances to drugs previously effective and require the substitution of other histamine antagonists; other patients who prove refractory to one of the more generally effective antihistamines will respond favorably to a drug universally less effective. Moreover, the degree and type of side effects produced by some of the more potent antihistamines will many times preclude their use.

There have been a number of attempts to overcome these drawbacks to effective therapy by combining antihistamines. Friedlaender and Friedlaender[2] found that although Antistine® provided symptomatic relief for 62.7 per cent of patients treated for allergic rhinitis and Pyribenzamine for 74.5 per cent, the combination of both proved effective in 91.2 per cent of cases. These findings suggest that besides the additive effect of the two drugs, there may possibly exist a synergism.

Arbesman *et al*[1] observed that many of the undesired side effects resulting from administration of an antihistamine could be eliminated by reducing the dosage. Simon and Toohey[4] consequently conducted a clinical study to determine the efficacy of a combination of two antihistaminic drugs, containings one half the average therapeutic dose of each. These investigators used Dibistine,® a combination of 25 mg tripelennamine hy-

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drochloride, (Pyribenzamine) and 50 mg. antazoline hydrochloride, (Antistine) in a series of fifty allergic cases. They observed improvement in 92 per cent of the patients and side effects consisting of slight drowsiness and depression in only 6 per cent.

Wittich[5] postulated that Dibistine would prove effective in a wide spectrum of allergic disease, since each of its components had shown advantages in specific allergic syndromes. On the other hand, the incidence of side effects induced by the combination would be diminished because of the decrease in dosage. He treated twenty-two grass-sensitive patients, the majority of whom had undergone some preseasonal immunization, with this product. During the period of treatment, a relatively toxic pollen was prevalent and there was an extremely high incidence of atmospheric mold offenders. The patients presented mild to moderate symptoms, depending on the extent of their immunization. Wittich[5] found that twenty of the series showed good results using coseasonal treatment with the combined antihistamine alone, and two showed moderate improvement. Two patients complained of some drowsiness or depression but not sufficient to discontinue treatment. Wittich treated thirty cases of seasonal allergic rhinitis and observed considerable improvement in twenty-six, and mild side effects in two patients. The combination controlled the pruritus in all of nine cases of atopic dermatitis, and was found to be useful in the later stages of preseasonal immunization. Dosage of pollen extract could be increased more rapidly without untoward reactions, thus insuring more adequate seasonal protection. Wittich concluded from these results that this combination is as effective as other antihistamines without causing as many side reactions.

The present study was undertaken in order to further investigate (1) the therapeutic effectiveness and (2) the incidence of untoward reactions to Dibistine* as compared to single antihistamine therapy. Two hundred and eleven allergic patients, forty-eight of whom had undergone previous treatment, were given the double antihistamine three times a day. These patients were observed in a Veterans Administration clinic and in private practice. The results are given in Table I.

DISCUSSION

In this series of patients, this product produced noteworthy results. It provided symptomatic relief in 99.5 per cent of patients and proved 73 per cent more effective than previous single antihistamine therapy. The incidence of side effects was less than half of that experienced previously.

Our satisfaction with its success must be tempered by knowledge of the variables which are likely to affect the results of a clinical study such as this. Geographical variation in pollen count and toxicity, variations in symptom threshold and emotional status of the patients, and normal cyclical

*Supplied through the courtesy of the Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

TABLE I

Condition	No. of Patients	Satisfactory Improvement
Perennial Allergic Rhinitis	118	118
Seasonal Allergic Rhinitis	74	74
Contact Dermatitis	14	14
Tinnitus	3	2
Total	211	210

Previous Antihistaminic Treatment Known	Relative Effectiveness of Dibistine Treatment		
	Better	Same	Less
48 Patients	35 (73%)	12 (25%)	1 (2%)

Side Effects Known in Previous Treatment	Dibistine Treatment		
	Mild	Moderate	Severe
34 Patients	3 (8.8%)	0	0

Incidence Side Effects in Total Series	Dibistine		
	Mild	Moderate	Severe
211 Patients	7 (3.3%)	0	0

variations of allergic symptoms all tend to exert an influence on results. Nevertheless, the almost complete therapeutic effectiveness of the double antihistamine provides further evidence of a possible mechanism of potentiating activity between its two components. On the other hand, the reduction of side effects can be attributed to the diminished dosage of each drug and a certain amount of antagonism of side effects.

CONCLUSIONS

A combination of 25 mg tripelennamine hydrochloride and 50 mg antazoline hydrochloride (Dibistine) was used in the treatment of 211 allergic patients.

Two hundred and ten patients reported satisfactory relief of symptoms and seven complained of mild side effects.

It produced less than half as many side effects and was found to be 73 per cent more effective than previous single antihistamine therapy.

The reduction of side effects can be attributed to the diminished dosage of each drug and a certain amount of antagonism of side effects.

Increased therapeutic effectiveness indicates a possible synergism between the components of this product.

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BOOKLET ON DRUG PRICES GETS ENTHUSIASTIC RESPONSE

A fourth printing of 250,000 copies of the National Pharmaceutical Council's new consumer booklet, "I Hate To Buy Drugs, But . . ," has been necessary to meet the demand by the drug industry and physicians, who requested 660,000 copies within one week after announcement that the booklet was available.

Publication of this booklet, written for the Council by Donald G. Cooley, well-known science writer, is part of NPC's public relations program. In the foreword, Dr. Theodore G. Klumpp, president of the Council, points out, "We are apt to forget that the values they [modern drugs] bring are bargains; and in many instances we can now purchase what neither love nor money could buy a short time ago. Every day we spend freely for things that are not necessities, much more indeed than for important drugs that add to our comfort, keep us healthy, overcome illness, and save our lives."

Copies of the booklet were mailed to the country's physicians, pharmacists, drug manufacturers and wholesalers, drug associations, state boards of pharmacy, colleges of pharmacy, opinion-making organizations, and science writers. The National Pharmaceutical Council was organized in 1954 to promote the best interests of the public, physicians, and the drug industry. Its members are: Abbott Laboratories, American Home Products Corporation, The Ames Company, Ciba Pharmaceutical Products, Geigy Pharmaceuticals, Hoffmann-LaRoche, Lederle Laboratories Division, McNeil Laboratories, Mead Johnson & Company, The Wm. S. Merrell Co., Chas. Pfizer & Co., G. D. Searle & Co., Smith, Kline & French Laboratories, E. R. Squibb & Sons, The Upjohn Company, Warner-Chilcott Laboratories, White Laboratories, and Winthrop Stearns.

VAGINAL AND URINARY SYMPTOMS FOLLOWING POLLEN INJECTIONS

Report of a Case

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REVIEW of the recent literature reveals nine cases of vulvo-vaginal pruritus associated with hay fever. All of these cases involved girls under twelve years of age.[1,2]

The following case is presented to emphasize that vaginal pruritus and urinary symptoms can result from pollen injections without actually accompanying hay fever symptoms during the pollen season.

CASE REPORT

This patient is a thirty-five-year-old white woman with a history of grass pollinosis of five years' duration. Her symptoms are present from the middle of May to the middle of July of each year, and consist of rhinitis, nasal blockage, conjunctivitis, and paroxysmal sneezing, but never any vulvo-vaginal symptoms during a pollen season.

She was first seen on April 21, 1953, at which time intradermal testing revealed a marked reaction to an equal mixture of timothy and orchard grass* (200 P.N.U./cc) and moderately positive reactions to sheep sorrel (200 P.N.U./cc), English plantain (200 P.N.U./cc), concentrated house dust, orris root and feathers. Subsequent testing showed moderately positive intradermal reactions to chicken, pork, peas, banana and lemon. Eight tests were done at one sitting. No tests were done for lamb, fish or oyster because of the patient's history of generalized urticaria after ingestion of these foods. Crab and lobster were not done because of her history of vulvular and vaginal itching after eating them.

Hyposensitization was carried out as follows: Our estimated skin test dose of pollen on April 21, 1953, was 2 protein nitrogen units of a timothy and orchard grass mixture, sheep sorrel and English plantain. The first subcutaneous dose of 5 protein nitrogen units of these mixed grasses was given on April 24, 1953. Two hours after this injection, very slight transient vulvular itching was noted. Ten protein nitrogen units were given on April 28 with no reaction. After this date, injections were given every three to four days until June 2. Dosage was increased by 50 per cent at each injection until a maximum dose of 100 protein nitrogen units was reached.

Concurrent dilute (1-10) house dust therapy was also used to a top dose of 5/10 cc. One hundred protein nitrogen units of pollen and 5/10 cc of dilute house dust were given at weekly intervals up to the middle of July. The last two injections at this dosage level caused severe pruritus vulvae which began four hours after the injections and lasted for twenty-four hours. Hay fever symptoms during this season were relieved ninety per cent.

Preseasonal treatment for the 1954 season was begun on January 8, 1954. A similar but somewhat more cautious regime of hyposensitization was carried out at weekly intervals. On February 17, 1954, at a dosage level of 25/100 cc of dilute house dust and 30 protein nitrogen units of pollen, a few hives on the back and abdomen appeared twenty minutes after the injection. At the next injection the dust was dropped

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Dr. Fox is an Associate Fellow of the American College of Allergists.
*Our pollen extracts are standardized in protein nitrogen units.

to 2/10 cc and pollen dosage was repeated at 30 protein nitrogen units, but the same reaction occurred. The dust was discontinued and the pollen dropped to 25 units with no reaction. At the next dose, however, on increasing the pollen to 30 units, severe vulvular and vaginal itching began four hours after the injection, continuing for twenty-four hours. This was associated with a marked burning on urination and urticaria of the abdomen and back which commenced four hours after the injection and lasted for one hour. Dosage was decreased to 10 protein nitrogen units at the next injection, and this was followed by intense itching of the vulva. This itching lasted for nine days, but was worse the first twenty-four hours. No treatment was given for fourteen days, during which time a urinalysis was negative and the blood sugar was normal.

The next pollen dosage was 2 protein nitrogen units which caused burning on urination but no genital itching; however, the patient did complain of a feeling of irritation in the pelvic area. To rule out any psychosomatic factors in this case, the next injection consisted of plain Coca's solution, following which no urticarial or genital reaction took place.

Dosage was reduced to 4/10 of one protein nitrogen unit. This dose was given at weekly intervals for five injections, and no genital or urinary symptoms occurred. The last dose was given on May 26. On June 16 and again on July 10, this patient reported a complete absence of pollen symptoms. These symptoms had been very severe in past years, which accounted for her unusual patience while we were obtaining dosage adjustment.

CONCLUSIONS

1. Genital and urinary symptoms can be caused by pollen injections.
2. It is possible to eliminate these reactions with a low dosage of pollen.
3. This low dose of pollen was enough to control hay fever in this very sensitive patient without producing untoward symptoms.

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CHANGE IN GENERIC NAMES OF NEW "METI" COMPOUNDS

In co-operation with and on the advice of the Council of Pharmacy and Chemistry of the American Medical Association, the generic names of the Schering Corporation's new "Meti" compounds have been changed. The generic name for "Meticorten" (metacortandracin) is now "prednisone," while that of "Meticortelone" (metacortandralone) is now "prednisolone."

MYCOLOGICAL FLORA OF THE AIR IN SAN JOSE, COSTA RICA, CENTRAL AMERICA

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THE PURPOSE of the present study is to present certain data on the frequency of fungus spores in the air of San José, Costa Rica, Central America, the importance of such spores in allergy disorders being well known.

Potato agar was prepared, with tartaric acid added to inhibit bacterial growth, and stored in test tubes in 15 cc portions. Isolation of the fungi was carried out by melting the contents of one tube in a hot water bath and pouring into a Petri dish.

Each dish was exposed to the air for five minutes, usually in the morning hours, in the same spot on the roof of a three-story building. In all, twenty-four samples were taken, totalling 453 fungus isolates. The samples were taken from March through August, 1954, March being a dry month while the other months are rainy. Isolates were transferred to 18 x 18 tubes of Sabouraud's glucose agar, and have been kept alive in the same medium or in a similar one, for eventual identification.

The 453 strains obtained comprise the following: *Cladosporium* 234 strains; *Penicillium* 60 strains; *Aspergillus* 23 strains; *Streptomyces* 7 strains; *Rhodotorula* 6 strains; *Mucor* 4 strains; *Trichoderma* 4 strains; *Fusarium* 2 strains; Helminthosporium 2 strains; *Rhizopus* 1 strain; *Paecilomyces* 1 strain; *Graphium* 1 strain; *Phialophora* 1 strain; *Stemphylium* 1 strain; *Trichothecium* 1 strain; *Yeast* 15 strains; *Dematiaceae steriles* 40 strains; *Mucedinaceae steriles* 20 strains and Undetermined, 34 strains.

The list shows the most abundant genus to be *Cladosporium*, which made up 51.6 per cent of the isolates, there being a large number of them in every Petri dish. The greatest number of *Cladosporium* isolated was obtained in March. *Penicillium* was second, with 13.2 per cent, and then *Aspergillus* with 5 per cent. The other molds occurred in much lower percentages. There were 8.8 per cent Dematiaceous and 4.4 per cent Mucedinaceous mycelia sterilia. The fifteen isolates of yeasts have not been determined to species, and there remain undetermined thirty-four other strains of various types.

Cladosporium has been shown to be the prevalent genus in other areas, as in New Brunswick, New Jersey, where Bruskin[2] found it to make up 49.1 per cent of isolates. In Cuba, Estrada de la Riva[3] found the predominant fungus to be *Hormodendrum* (= *Cladosporium*), as did Almeida et al [1] in Sao Paulo, Brazil. Negroni[4] in Buenos Aires, Argentina, found

Penicillium to be the most frequent genus, although on a percentage basis *Cladosporium* gave 25.7 per cent as against 23.9 per cent for *Penicillium*.

SUMMARY

The isolation of 453 strains of molds from the air in San Jose, Costa Rica, Central America, is reported in the months from March through August, 1954. *Cladosporium* was found to be the prevalent genus, with 51.6 per cent of isolates. Next in frequency were *Penicillium* with 13.2 per cent and *Aspergillus* with 5 per cent.

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AIR POLLUTION FOUNDATION DEVELOPS FIRST CONTINUOUS OZONE MEASURING INSTRUMENT

For the first time in scientific annals, a photoelectric instrument has been developed for the automatic, around-the-clock measurement of ozone—the poisonous, smelly gas suspected of being the major cause of smog in the Los Angeles atmosphere.

Development of the new device, which has been nearly a year in the making, has been announced by Dr. Lauren B. Hitchcock, president and managing director of the Air Pollution Foundation, who called it "an historic chapter in the battle against smog."

The first of these devices, which was conceived, developed, and built by the Air Pollution Foundation, has just been placed in operation in North Hollywood. The design of the new instrument has been made available to the County Air Pollution Control District, which already has ordered the construction of three additional devices.

According to Dr. Hitchcock, the device will determine how much poisonous ozone there is in the Los Angeles air and where most of the concentrations of ozone occur. He said that removal of ozone from the air might possibly do away with the eye-irritating effects of smog, even though other pollutants remain.

INTRAVENOUS HYDROCORTISONE IN ALLERGY

Preliminary Report

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ADRENAL corticosteroid therapy is now well accepted in allergy and has proved most useful in certain instances. It is now known that hydrocortisone (17-hydroxycorticosterone) represents one of the most active components secreted by the adrenal cortex, and is available in the oral, intramuscular and, lately, in the intravenous dosage forms.

The intravenous hydrocortisone* used in this series consists of the free alcohol form in 100 mg/20 cc ampul in 50 per cent alcohol. This is diluted before using in 1000 cc of 5 per cent dextrose and given slowly over a period of time. As much as 50 mg/hr has been given without untoward effect.[3]

The relative speed of action of the oral, intramuscular and intravenous routes of hydrocortisone has been compared.[2] The acetate ester is somewhat more slowly absorbed than the more soluble free alcohol. When hydrocortisone is given orally, there is a rise in the plasma 17-hydroxycorticoids with a peak in about one hour and a return to control level in four to eight hours. Thorn et al[4] gave a patient intravenous hydrocortisone at the rate of 12 mg/hr for eight hours and noted eosinopenia and a rise in urinary potassium in one hour. Other metabolic effects, such as rise in blood sugar, et cetera, occurred later. According to Cochran and co-workers,[2] intravenous hydrocortisone has a demonstrable effect on the eosinophils in one hour and a major effect in three hours, with a residual effect for twenty-four hours. This compares with the demonstrable effect of oral hydrocortisone in three hours and a maximal effect in eight hours. Oral cortisone effect was about like that of oral hydrocortisone but less effective as would be expected. The intramuscular route was inefficient and slower.

While laboratory determinations are of great value, they do not always parallel the clinical picture. Thus, it becomes necessary for the clinician to determine the speed of action in the disorders under investigation. Bickerman and Barach[1] studied the comparative results of the use of ACTH, cortisone and hydrocortisone in the treatment of asthma. They noted that in the majority, the relief of bronchospasm occurred eighteen to thirty-six hours after oral hydrocortisone, twenty-four to forty-eight hours after ACTH gel, and four to five days after oral cortisone.

With these thoughts in mind, an attempt was made to determine the speed of action of intravenous hydrocortisone. Patients with moderately

*This material was generously provided by the Upjohn Company.

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TABLE I.

Case	Dose	Time	Vital Capacity cc	Maximal Breathing Capacity cc/min.	Total Eosinophil Count min.[4]	Remarks
(1) M.V.	200 mg	Base	3000	45,000	921	Asthma prompted by infection: Adrenalin resistant.
		1 hr.	3100	54,000	591	
		2 hr.	3000	52,800	244	Therapy effective.
		3 hr.	3000	63,000	377	
		4 hr.	3500	64,200	235	
		5 hr.	3500	63,800	45	
		6 hr.	4200	91,000	11	
(2) G.H.	300 mg	Base	1100	18,000	477	Intrinsic asthma: Adrenalin resistant Hyperventilating
		1 hr.	1100	17,600	355	
		2 hr.	1200	22,800	188	Therapy not effective 6 hr. period followed with oral hydrocortisone
		3 hr.	1200	21,000	44	
		4 hr.	1000	12,000	33	Effective in 2 days.
		5 hr.	1200	21,000	10	
		6 hr.	1200	18,000	0	
(3) N.P.	100 mg	Base	1400	18,000	1200	Intrinsic asthma.
		1 hr.	1450	18,000	440	Therapy effective.
		2 hr.	1500	21,000	520	
		3 hr.	1500	22,000	180	
		4 hr.	1475	22,600	160	
		5 hr.	2000	60,000	60	
		6 hr.	2400	72,000	16	
(4) R.C.	200 mg	Base	1000	22,000	620	70-year-old intrinsic asthmatic hospitalized: Asthma severe.
		1 hr.	1000	22,400	600	
		2 hr.	1050	22,000	672	Therapy not effective.
		3 hr.	1050	22,000	504	
		4 hr.	1100	26,000	112	
		5 hr.	1350	30,400	12	
		6 hr.	1950	36,800	0	
(5) R.F.	200 mg	Base	1800	28,400	1420	11-year-old boy, dust bacteria: Moderate asthma.
		1 hr.	1800	28,000	760	
		2 hr.	2000	34,000	215	Therapy effective.
		3 hr.	2200	40,800	211	
		4 hr.	2200	41,200	18	
		5 hr.	2400	47,400	0	
		6 hr.	2650	58,800	0	
(6) R.E.	200 mg	Base	1600	24,000	672	10-year-old boy, dust definite: Asthma moderate.
		1 hr.	1550	24,000	728	
		2 hr.	1600	24,400	540	Therapy effective.
		3 hr.	1600	24,300	110	
		4 hr.	1800	28,800	84	
		5 hr.	1950	36,200	24	
		6 hr.	2150	48,400	24	

severe asthma were selected, who were willing to be hospitalized and who had previous training with pulmonary function tests. A base line was then determined on the vital capacity, maximal breathing capacity, and total eosinophil count. From 100 to 300 mg of hydrocortisone was infused over a six-hour period. The determinations were made hourly. At the end of the experiment, the patients were started on oral hydrocortisone.

RESULTS

The results were carefully recorded on six asthmatic patients (Table I.) All showed significant to complete eosinopenia within the six hours. A significant fall in eosinophils was noted in one hour in three of the six cases. The vital capacity and maximal breathing capacity changes closely paralleled each other and were in line with the objective and subjective findings on the patient. As is expected, the changes in maximal breathing capacity were much more dramatic. Therapy was classified as effective

with approximately a two-fold increase in maximal breathing capacity, together with subjective and objective signs of improvement as noted by the patient and the physician. Of the six patients, therapy was classified as effective in four. Most of the changes were noted in the fifth and sixth hours, although one patient had a doubling of the MBC in three hours. The two patients in whom therapy was not effective in six hours responded to oral hydrocortisone in doses of 60 mg every six hours in forty-eight hours.

One patient having severe urticaria with laryngeal edema was given 200 mg of hydrocortisone intravenously over a fourteen-hour period. She had previously responded fairly well to ACTH, though not to adrenalin or antihistamines. She was hospitalized, and measurement showed the wheals to be 1 x ½ cm in certain portions of her body. These wheals had been fairly constant for several days. In one hour there was subjective improvement of the itching and the wheals had decreased in diameter to ½ x ¼ cm with less reddening. In five hours the urticaria had disappeared completely. The patient was placed on oral hydrocortisone maintenance. It was interesting to note that 40 mg every six hours orally was less effective than the previous intravenous dosage, as she continued to have mild bouts of urticaria.

DISCUSSION

From the preliminary observations noted here, it can be concluded that intravenous hydrocortisone is an effective and swiftly-acting therapy in some patients with asthma. Much more data would be necessary to draw any more definite conclusions. It would be interesting to compare the speed of action in different types of asthma, such as pollen asthma and asthma associated with infection.

It is the feeling of some investigators[3] that, following the intravenous use of hydrocortisone, additional oral or intramuscular material should be supplied within two to four hours and in gradually increasing dosage thereafter. They believe the high blood levels attained suppress pituitary corticotropin secretion. After an eight-hour infusion, this may last thirty-six hours as judged by the output of 17-hydroxycorticoids.

It is obvious that intravenous hydrocortisone is the therapy of choice in acute adrenal cortical insufficiency. While this is not primarily in the province of the allergist, he may well see such a condition following the discontinuance of long-term corticosteroid therapy. This is particularly true if stress such as provided by a surgical operation or severe infection intervenes. In such a case, intravenous hydrocortisone may be lifesaving.

SUMMARY

The infusion of 100 to 300 mg of intravenous hydrocortisone over a six-hour period had a definite beneficial effect in four of six asthmatic patients.

From these preliminary observations, it is probable that intravenous hydrocortisone will find a limited but definite place in treatment of acute allergic reactions. It will be most useful in those situations in which speed and maximal effect are of importance. Certainly this mode of therapy deserves further consideration.

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EXPERIMENTAL DRUGS TO CONTROL ATTACKS OF ASTHMA STUDIED IN GUINEA PIGS WITH AID OF SPECIAL CHAMBER

At Lakeside Laboratories in Milwaukee, Wisconsin, experiments are being made to test the effectiveness of certain drugs in preventing attacks of bronchial asthma. An "aerosol chamber" for guinea pigs, which was first used to test the effectiveness of antihistamines, is being used in this study. Guinea pigs were selected because the musculature of their bronchial tubes seems most susceptible to drugs whose effects "mimic" asthmatic attacks. Four guinea pigs are placed in four separate compartments under a bell jar on a stand, and compressed air is blown upward under constant pressure, through a nebulizer containing a solution of histamine or acetylcholine, producing symptoms of asthma. The animals are standardized so their reactions to the symptom-producing drugs can be anticipated. Usually 90 per cent of the guinea pigs will develop severe asthmatic symptoms when histamine or acetylcholine is introduced into the chamber. They are then given an experimental drug by stomach tube, to see if it will help control the "attack." Three-quarters of an hour later they are placed in the compartments and subjected to aerosol spray. Several hours later, the histamine or acetylcholine spray is used again to test the effectiveness of the drug for prolonged action.

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

PENICILLIN PROPHYLAXIS IN PEDIATRIC PRACTICE

PUBLISHED in the present issue is a report on the incidence of allergic reaction to penicillin in infants and children and of penicillin prophylaxis by Dr. Joseph H. Lapin. Here the author reviews the literature on penicillin reactions pointing out that they are fairly rare in children though fairly common in adults, and reports a study on penicillin prophylaxis carried out on 402 infants and children seen in private practice.

Although this study has been carefully done it should be pointed out here that there are aspects of it which are highly controversial. Most allergists would agree with the author that parents can be reassured that when penicillin is given to their children there is very little likelihood of their having a serious reaction. They would also agree that oral penicillin should be used when possible and intramuscular penicillin used rather than oral penicillin for severe infections or where there is vomiting of the drug.

The controversial issue arises when one uses penicillin as prophylaxis routinely in respiratory infections in infants and children. As all pediatric allergists know, a great many infants and children suffer from mild respiratory infections which can be cleared up without the use of any antibiotic at all and without any resulting complications. The question therefore arises whether it is worth while to give penicillin routinely in all of these infections in the hope of preventing the complications of nephritis et cetera, but at the risk of having the complication of penicillin sensitivity. Dr. Lapin concludes that it is. However, many pediatricians and pediatric allergists would disagree with him feeling that in the mild infections no antibiotic should be used and in the more severe infections one should use one of the other antibiotics which can be given orally, reserving penicillin either to treat complications or for more severe infections, since this is the only drug which it is practical to give intramuscularly in home or office practice.

These remarks do not, however, apply to a child who has suffered from rheumatic fever or nephritis, where the use of penicillin for even very minor respiratory infections, most of us will agree, is quite justified.—C.C.W.

Progress in Allergy

PEDIATRIC ALLERGY

A Critical Review

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and

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This review of the literature on pediatric allergy and the literature of interest to pediatric allergists continues from the review published last year under the same title[20] and includes work published during the latter months of 1953 and the major part of 1954.

DERMATOLOGIC ALLERGY

As might be expected, the recent literature on dermatologic allergy deals mostly with the use of cortisone preparations. Solomons[89] reports fifteen cases of infantile eczema all under three years of age who were treated with cortisone, usually in doses not exceeding 75 mgms a day. In six the response was slow, unconvincing and not maintained. In another six there was a moderately good response and in the remaining three there was a very satisfying response. The author points out that there seems to be very little justification for administering cortisone to infants with eczema unless the lesions are severe, the infants' general health is deteriorating and scratching has become severe. He stresses that this drug gives symptomatic relief only.

McCorriston[63] reports the use of hydrocortisone acetate ointment in eczema of infants and children. He summarizes the results of treatment by topical application to 104 infants and children with eczema with the ointment in either 1 per cent or 2.5 per cent concentration in various ointment bases. The cases, in general, had very severe eczema. In a number of them, control areas were kept for comparison. It was found in many that improvement occurred within twenty-four to forty-eight hours and, following improvement, the patients were much more comfortable and the amount of ointment required could be greatly reduced. It was noted that 75 to 100 per cent good effect was obtained in all cases with the proper bases, and improvement was maintained with therapy and subsequently maintained in most periods for considerable periods of time after cessation of therapy. Flare-ups were also easier to control. The author feels that this agent is the single, most effective one in the treatment of eczema in infants and children and no contraindications to the use of the ointment were found. There seemed to be little or no absorption, at least not enough absorption to produce adverse systemic effects. No cases of allergic hypersensitivity to the ointment were noted.

Witten et al[97] report the use of 2½ per cent hydrocortisone ointment

From the Allergy Clinic, Hospital for Sick Children, and the Department of Pediatrics, University of Toronto, Canada; and the New York Medical College and Flower and Fifth Avenue Hospitals, New York.

on thirty patients with infantile eczema varying in age from four months to six years, but most of them were under two years. All were treated with the application of the ointment to one-half of the body and a control ointment to the other half of the body. Of the thirty cases, eighteen showed improvement with the ointment, five showed no improvement and seven showed equal improvement with both the ointment and the control ointment. There were no instances of intolerance to the ointment and there was no evidence of absorption of the hydrocortisone even though, in nine infants under fourteen months of age, approximately one-half or more of the body surface had the ointment applied to it two or three times a day for one to seven weeks without a single instance of clinical toxicity.

Robinson and Robinson[76] report 172 cases of atopic dermatitis which were treated with hydrocortisone acetate ointment. A concentration of less than 1 per cent was found to be relatively ineffective but 2½ per cent gave very good results. Of the 172 cases, 144 had complete relief of symptoms and involution of lesions for the duration of the administration of the medication but in all instances relapse occurred when therapy was discontinued. Partial temporary benefit occurred in six other cases, and twenty-two persons were not benefited. In a total of 418 cases of dermatosis, including non-allergic dermatosis, adverse reactions to the ointment was found in thirty-eight cases. The authors do not state how many of these occurred in the cases of atopic dermatitis.

Friedlaender and Friedlaender[34] studied the topical use of hydrocortisone and hydrocortisone-neomycin ointment in allergic dermatoses, using the 2½ per cent hydrocortisone (alcohol) ointment, 2½ per cent hydrocortisone acetate ointment, 1 per cent hydrocortisone acetate ointment, a placebo base, 1 per cent hydrocortisone acetate ointment with neomycin sulphate ½ per cent and 2½ per cent hydrocortisone acetate ointment with neomycin sulphate ½ per cent. They also used the ½ per cent neomycin sulphate ointment alone. They found that when improvement occurred with the ointment it was usually rapid, often evident in the first twenty-four to forty-eight hours, progressing to a maximum response by the end of the first week of treatment. They did not find any difference between the efficacy of the hydrocortisone alcohol and the hydrocortisone acetate ointments in fifteen patients. They treated seventy-three patients with atopic dermatitis, twenty-nine of whom were infants and children. Of the adults, twenty of thirty-seven initially given the 2½ per cent ointment showed a marked improvement, eleven were benefited less and no help occurred in three. Aggravation of the dermatitis was recorded in three others. The 1 per cent ointment was not effective. In fifteen infants and children initially given the 2½ per cent ointment nine showed marked improvement, four showed slight to moderate improvement and two showed no improvement. In fourteen children there was an initial marked improvement in eleven, two showed only slight to moderate improvement and one no improvement at all with 1 per cent ointment. Approximately one-third benefited by the 2½ per cent ointment and were similiarly helped by the 1 per cent concentration, the remainder had less favorable responses. They found that the lesions of atopic dermatitis usually encountered in infants and children were more readily influenced by the ointment than were those in adults, and that the 1 per cent ointment was frequently sufficient for children. They also studied thirty patients with contact dermatitis. The 2½ per cent ointment and 1 per cent ointment gave excellent results in sixteen, slight to moderate results in ten and negligible improvement in three. One patient was made worse by the ap-

plication of the ointment. They made a separate study of twenty-nine cases with dermatitis of the hands who did not have lesions elsewhere in the skin. In twenty-two with chronic eczema of the hands, six gave a favourable response, eight a less favourable response, five were not helped and three became worse. In contact dermatitis limited to the hands, some degree of improvement was recorded in four out of five. Since many of the lesions were infected at the time of treatment or became infected during the treatment, they studied the hydrocortisone-neomycin combination on thirty patients who had dermatoses complicated by secondary infection. Fourteen achieved a more rapid improvement of both the infection and the underlying dermatosis in the areas treated with the antibiotic-containing ointment. In the entire group of 159 patients the dermatitis became worse in nine. At least six of these were felt to be sensitive to the ointment base and this was confirmed by patch tests, and in two patients the skin appeared to be irritated by the use of an ointment during an acute phase of dermatitis where bland local therapy would have probably been more suitable. In one patient the cause of aggravation was not determined. The authors stress the fact that, although these ointments give effective symptomatic relief and are therefore very useful, they should not replace proper antiallergic management to obtain lasting benefit.

The conclusions that one would come to from these papers is that hydrocortisone ointment as opposed to cortisone ointment is very effective in relieving the symptoms of atopic dermatitis but that it is not an end in itself, merely symptomatic therapy.

Sulzberger and Witten[93] discuss prolonged therapy with cortisone for chronic skin diseases and define long term therapy as that lasting for two months or longer. Of the thirty-five cases reported, only fifteen were atopic dermatitis and only these will be discussed here. Of these fifteen cases, three were children. The dosage used was usually high, initially in the neighborhood of 150 to 200 mgms daily but was rapidly decreased to a maintenance dosage, which was usually around 25 mgms daily, sometimes higher. The authors feel that there is little danger of serious effects if the maintenance dose is 75 mgms a day or lower, and that this form of therapy is very effective. The authors feel that in this study which was of four years' duration, there was no evidence of acquired drug resistance and therefore no necessity for progressive and continued increase in dosage of cortisone. Neither was there any addiction to the drug. They feel that cases which receive long term therapy should be only the very severe ones, which do not respond to other methods of treatment and in whom the disease is so severe that the lives of the patients and of their families are suffering greatly.

Alcorn[5] has written a general discussion of infantile eczema and as it is itself a review it will not be further reviewed here.

Two papers have occurred on purpura. The first by Ackroyd[2] is a very complete review. The author divides allergic purpura into two types, one of which is purpura associated with an erythematous exanthem and joint and visceral symptoms, the so-called Schönlein-Henoch syndrome. Although he classifies this with allergic purpura, he points out that apart from a very small proportion of cases which are due to food and are truly allergic, the cause of the condition is unknown and its allergic origin entirely unproved. The second group consists of true purpura which is never exanthematous, that is the surrounding skin is normal. It may be caused by infections, drugs and occasionally certain other substances possibly including foods in very rare cases. In a very complete discussion of the

Schönlein-Henoch syndrome he points out that ACTH has been tried with equivocal results. With regard to the role of infection he says it is believed that this syndrome is a manifestation of bacterial allergy, particularly due to the streptococcus, but the evidence for this is inconclusive. He reviews the literature on Schönlein-Henoch syndrome due to hypersensitivity to foods and lists in table form the twenty-three cases which have been reported in the literature. In every one of these cases removal of the offending food from the diet was followed by cessation of symptoms. Egg, milk, chocolate, wheat and beans have been most frequently implicated, with a large variety of foods as occasional causes. In a discussion of purpura due to infections he lists the various types of infection that can cause this syndrome, pointing out that the purpura apparently bears no relationship to the severity of the primary disease and may complicate mild or severe infections. He points out that it is impossible in any individual case to prove the relationship between purpura and infection but, nonetheless, the occurrence of a brief episode of purpura followed by complete recovery in a patient who never had any hemorrhagic symptoms before and who is suffering from or who has recently recovered from an infection, constitutes strong presumptive evidence that the purpura was due to the infection. Next he discusses purpura due to drugs, pointing out that this is uncommon but has been reported with a large number of different drugs which are listed. Foods apparently hardly ever cause this type of purpura, although some cases have been reported. He describes in detail the *in vitro* tests which can be used to detect hypersensitivity to Sedormid.® These investigations show that Sedormid causes platelet lysis in the blood of sensitized patients and this is presumably the cause of the thrombocytopenia in Sedormid purpura. It is not known how far these findings are applicable to thrombocytopenic purpura due to other drugs, but it is presumed that the underlying mechanism may be similar. This is a very complete and useful review of the subject of purpura.

Adamson et al[1] report three cases of idiopathic thrombocytopenic purpura treated with cortisone and ACTH. One responded, the other two did not, but the two cases which did not responded to splenectomy. The authors also review the literature on this condition, pointing out that ACTH and cortisone have been effective in reversing the hematologic changes in idiopathic thrombocytopenic purpura in most reported studies. Cortisone on the whole has been more effective than ACTH in this condition. They feel that in idiopathic thrombocytopenic purpura a trial of ACTH and cortisone is of practical value as a preparation for splenectomy and to tide the patient over a critical bleeding episode. They also describe one case of Schönlein-Henoch purpura which responded dramatically to small doses of ACTH and oral cortisone, and from the literature conclude that ACTH and cortisone have proved efficacious in the great majority of cases of Schönlein-Henoch purpura. In the purpuric stage they feel that oral cortisone is preferable to ACTH by injection. Three of the reported cases were children, one was an adult.

Two papers have appeared on the treatment of poison ivy. Goldman and Preston[44] report forty-seven patients with poison ivy dermatitis who were treated with hydrocortisone orally and with hydrocortisone ointment or lotion. They conclude from their study and previous work that hydrocortisone orally is, dosage by dosage, more effective than cortisone given orally, and they feel that the hydrocortisone is almost twice as effective. They feel that hydrocortisone ointment is of considerable value in the

treatment of this condition and that the lanolin base hydrocortisone ointment is more effective locally than the hydrocortisone in other bases. Parish[71] reports the use of Prantal® in the treatment of seventy-three cases of poison ivy dermatitis. This substance is a new synthetic anticholinergic drug with a low incidence of undesirable side effects. The drug was given by the oral route daily in divided doses. Included in the study were twenty-six children who received 50 mgms three times daily, ten adults who were given 100 mgms three times daily and thirty-seven adults who received 100 mgms four times daily. Controls consisted of patients who had been treated prior to the availability of the drug. Most patients reported relief of the itching in twelve to twenty-four hours, oozing stopped in forty-eight hours and the lesions cleared completely in three to five days. No undesirable side effects were observed. The author concludes that the drug is very useful in the treatment of poison ivy dermatitis and is well tolerated both by infants and children.

Siegel and Bergeron[85] discuss urticaria and angioedema in children and adults. They report 115 cases of acute and chronic urticaria and angioedema, all of whom were thirty-four years of age or younger and forty of whom were children. Thirty-nine had chronic symptoms, that is urticaria lasting longer than a month, and seventy-six were in the acute stage. Penicillin was found to be the most common cause and was responsible for 24 per cent of the cases. In 12 per cent the cause of urticaria and angioedema was foods. Infection was considered to be the primary or initiating factor in 10 per cent. In 31 per cent of the cases the etiology could not be determined. Ninety-eight patients had electrocardiograms done during the acute phase of urticaria and angioedema and in no case was any abnormality detected which could be considered due to the primary condition. The authors conclude from this that pathologic changes in the heart as manifested by abnormal electrocardiograms are rare in these conditions and, therefore, this could be helpful in distinguishing these conditions from such things as serum sickness, collagen disease and rheumatic fever.

Barrow[9] reviews the literature on the virus of herpes simplex in infantile eczema and reports two cases infected with this virus. He also reports one case of a vaccination complicating infantile eczema. He discusses the diagnosis, treatment, prognosis, communicability and prevention of these conditions, and points out that it should be possible in the majority of cases to distinguish clinically between the two conditions. The differentiating points are listed. This article again emphasizes two important complications of infantile eczema, and stresses the necessity for protecting patients suffering from this disease from these two types of virus.

Pettit[72] reports a study on childhood eczema with and without the use of unsaturated fatty acids in treatment. The first series consisted of twenty-seven patients with atopic eczema ranging in age from eighteen months to fifteen years. Fifteen of the children were given unsaturated fatty acids locally in an ointment, as well as orally, and the other twelve served as controls. In the second series of thirty-six cases, twenty received the unsaturated fatty acids by mouth only for several months, and the other sixteen received only routine treatment. They found that the cases treated with the unsaturated fatty acids did no better than those who were not treated in this manner. This paper is in keeping with the general feeling at present on the lack of value of unsaturated fatty acids in the treatment of eczema.

Nelson and Stoesser[68] discuss the effect of soaps and related products

on the skin. They point out that the ordinary soaps may act as irritants to the skin, the irritation being due to the alkalinizing effects of the soap and builders in the soap and also to the irritating fatty acids, dyes, preservatives, perfumes, bleaches, germicides and medicinal agents. They feel that soap substitutes such as demulcents and cleansing oils are unsatisfactory agents and the so-called detergents are also unsatisfactory. However, they found that a product sold commercially as Lowila® cake or Lowila liquid is relatively hypo-allergenic, non-irritating to the skin, and valuable in the treatment of the child with eczema, for the delicate skin of the premature or for the skin involved with heat rash or ammoniacal dermatitis.

Friedlaender and Friedlaender[33] studied the topical use of an ointment made with a combination of tar and antihistamine in sixty-seven cases of chronic dermatitis, fifty-four of which suffered from atopic eczema. Thirty-five out of the fifty-four obtained some symptomatic relief from the application, and it was found in many of the patients that the combination was more effective than any of the individual ingredients.

RESPIRATORY ALLERGY

As in the case of dermatologic allergy, the major portion of the literature on the subject of respiratory allergy this year has been confined to the use of cortisone, ACTH and hydrocortisone. Irwin et al[52] report twenty-two patients, all adults, suffering from constant, intractable perennial asthma of unknown etiology who could not be controlled by the conventional methods of treatment, who were treated with cortisone on a long-term basis, usually with a high dosage initially and a maintenance dose in the neighbourhood of 75 to 100 mgms a day. They found that all or practically all of such patients can be relieved of their symptoms and maintained symptom-free with this medication. They emphasized that the patients must be watched closely for complications. It is important to make determinations of urinary calcium excretion and periodic spine roentgenograms as useful guides for predicting which of the patients will develop clinical osteoporosis.

Gelfand[38] reports the prolonged administration of cortisone and ACTH in twenty-seven ambulatory patients, eighteen with bronchial asthma and nine with allergic dermatitis. All the patients were adults and for many years had been suffering from severe allergic disease which had resisted conventional methods of treatment. The patients were given cortisone starting in a high dosage which was reduced as rapidly as possible to a maintenance dose, even as low as 12½ mgms daily or every other day, and in addition 10 or 20 units of ACTH gel were given once or twice a week. No significant side reactions were observed with the eighteen patients with bronchial asthma, and only one failed to show considerable improvement. Of the nine cases of dermatitis all showed excellent improvement. The author concludes that these drugs are very useful in the care of allergic patients of this type.

Ball[8] reports a controlled series of thirteen patients with severe chronic asthma who were given either corticotrophin or saline solution by injection for twelve days, not knowing which they were receiving. Of six patients receiving the former, five showed moderate or much improvement compared with two out of seven patients receiving the latter. Relapse was prompt in many of the patients when the drug was withdrawn.

Seven patients in the trial group and five patients with status asthmaticus were maintained on corticotrophin for from one to thirteen months, with an average of six months, and results were usually satisfactory.

Herxheimer[50] studied the amount of inhaled allergen causing mild attacks of asthma in eighteen experiments on eleven adult asthmatic patients. The patients were given cortisone and when under its full influence were exposed to double or treble the amount of the same allergen. This exposure was repeated when cortisone dosage had been reduced and again after the cortisone influence had ceased. The doubling or trebling of the amount of inhaled allergen, which normally would have caused a violent and severe attack, caused under cortisone influence either very mild and transient attacks or in the late reactors no attack at all. The same exposure under reduced cortisone dosage had the same result and this did not change after the administration of cortisone. In the immediate reactions the asthma attack tended to become still milder towards the end of the experiment, until it finally disappeared when the exposure was repeated a second or third time after omission of cortisone. The author concludes from this that in most moderate and mild cases of asthma cortisone protects the patient from the violent attacks due to overexposure. Moreover, he believes that it prevents the otherwise unavoidable hypersensitization which follows the administration of large doses of allergen and permits hyposensitization to develop in spite of overdosage. He therefore feels that cortisone can be used to speed up the process of hyposensitization.

Although the author's conclusions follow logically from his experiment, the conclusions are based on the premise that exposure to large amounts of allergen is necessary in order to accomplish hyposensitization. On the other hand, there are allergists who believe that exposure to very small doses of allergen can produce effective hyposensitization without having either any clinical reactions to the administration of the allergen or any period of hypersensitization such as the author describes as following larger doses of allergen. Therefore, it, would seem more logical to hyposensitize the patients using small doses which are small enough not to produce clinical reactions or the period of hypersensitization rather than using cortisone.

Bickerman and Barack[14] report 163 patients, 107 of whom are suffering from chronic intractable asthma and fifty-six from severe pulmonary emphysema, who were given 309 courses of ACTH and cortisone or hydrocortisone. Complete or partial remission was observed in 82 per cent of the ACTH courses, 86 per cent of the cortisone courses and 96 per cent of the hydrocortisone courses, the latter having been administered at a dosage level averaging 50 to 60 per cent of that employed with cortisone. The duration of the remission induced by short intensive courses of these drugs was generally short lived, averaging approximately two to three weeks. The patients with bronchial asthma generally manifested a more complete remission than those with the bronchospastic type of pulmonary emphysema. Best results were obtained in those with persistent bronchospasm as a result of exposure to seasonal factors, such as pollens, and patients in whom the asthmatic state had been previously well controlled but in whom intractable bronchospasm developed following an upper respiratory infection.

Fyles and Rose[36] report on the treatment of fifteen cases of asthma, varying in age from six to fifty-nine years, with use of oral hydrocortisone. Symptoms began to subside in twenty-four to seventy-two hours, and subsequent improvement was rapid. Fourteen patients became reason-

ably free of symptoms in a few days. In several of these cases the maintenance dose was found to be between twenty and forty mgms daily. The usual dose of hydrocortisone was found to be four-fifths of the dose of cortisone expressed in mgms. Side effects were no greater than with cortisone and the duration of relief following cessation of therapy was similiar with the two drugs. They point out that hydrocortisone seems to be just as effective as cortisone in the control of asthma.

Schwartz[83] reports thirty-nine patients with bronchial asthma and ten patients with ragweed hay fever who were treated with oral hydrocortisone tablets. Of the thirty-nine asthmatic patients, twenty obtained excellent relief of symptoms, four patients failed to respond and the remainder had some relief. Of the ten ragweed hay fever patients, seven obtained excellent relief, the other three some relief. The response to hydrocortisone orally was found to be as effective in fifteen of twenty-four patients as with cortisone, and superior in eight others. One patient failed to respond to either. Significant side reactions requiring discontinuation of therapy were observed in only two patients. Many of this series were children. In general therapy was initiated with a daily dose of 80 mgms and rapidly reduced to a maintenance dose of 40 to 60 mgms. The daily dose was administered in four divided doses following each meal and at bedtime.

Traynor et al[96] report thirteen cases of ragweed hay fever who were treated during one ragweed pollen season with hydrocortisone. These patients had not been doing well with other methods of treatment. All patients obtained very definite relief from their symptoms, usually within forty-eight hours after administration of the drug. The dose varied, but the usual initial dose was 80 mgms daily, divided at six or eight hour intervals. Frequently after the drug had been given for approximately five days it could be stopped without recurrence of symptoms unless asthma was also present. The asthma did tend to recur as soon as the drug was stopped. The authors conclude that use of hydrocortisone in pollinosis appears justified in certain carefully selected cases and could be expected to produce benefit with a minimal risk of untoward reactions.

Schwarz[84] reports on the use of intranasal corticotrophin in thirteen consecutive patients with acute hay fever and two patients with allergic rhinitis. This was given as a powder mixed with bacitracin and tyrothricin. The preparation was administered as a snuff in a dosage varying from 40 to 100 units daily, given in divided doses of 20 units each. The effective maintenance dosage ranged from 5 to 20 units daily. All patients showed considerable improvement. In three cases it was necessary to discontinue the treatment, in two because of allergic reactions. The authors conclude that this is an effective method of treatment of allergic rhinitis and hay fever.

Stewart and Kawa[92] report on the use of cortisone and ACTH in the treatment of allergic rhinitis. They had fifty-six cases, exclusive of hay fever. In fifty-four of the fifty-six cases tissue was taken from the inferior turbinate of the nose prior to commencement of treatment, and the histopathology of these sections compared with similar tissue from nonallergic individuals. The paper contains several excellent photomicrographs of these. Of the fifty-six patients, twenty-six were free of symptoms, sixteen were much improved, thirteen were improved, and the treatment was a failure in one. The authors conclude that ACTH and cortisone are very valuable in the relief of this condition. In this paper no mention is made of skin testing and appropriate hyposensitization therapy. However, presumably this was done, and it should be stressed

that these drugs are of symptomatic value only and should never be used to replace generally accepted proper antiallergic therapy.

Robertson and Sinclair[75] review the literature on fatal bronchial asthma pointing out that very few cases have been reported. They report eighteen cases which have been studied at autopsy, and describe two modes of death. In the one, death followed a severe resistant attack of bronchospasm; in the other there was sudden death of the asthmatic patient during the attack. They review treatment of these cases and again point out that morphine should never be used. They also stress the importance of mucus plugs in the bronchi, and this was present in all their cases. They emphasize that iodides are very helpful in the relief of this condition.

Prince, Etter and Jackson[73] describe the use of aerosol trypsin therapy in the treatment of asthma. They report on seventeen patients, nine suffering from atopic bronchial asthma with secondary infection and eight with primary infectious asthma. All were adults. Initially the patients received some aerosol epinephrine followed by the trypsin, usually in a dosage of 125,000 units. The patients received from one to ten treatments. Although some patients were benefited, the general conclusion of the authors was that trypsin was of little use in these patients. They point out that it would be reasonable to expect the trypsin to offer more therapeutic aid in patients with respiratory infections who were not allergic, because in the allergic individuals there is a continuous stimulus for more mucus to be formed.

Brown and Colombo[15] review the literature on allergy to odors, smells and fumes. They describe a questionnaire which they have prepared for patients to fill out describing the effects of odors, smells, fumes and drugs on their allergy. They report that their first patient with bronchospasm, unequivocally due to exposure to the fumes of range oil and nothing else, was seen approximately ten years ago and since that time they have gathered data on 200 patients in whom fumes, odors and smells caused major symptoms which could be brought on by exposure and relieved by elimination, in some cases resulting in complete and lasting relief. This of course demonstrates that such effects should be sought in all allergic histories. They note that approximately 85 per cent of asthmatic patients are not markedly affected by odors, fumes, smells or drugs. Those who do report such effects report them as varying from slight annoyance to major symptoms, sometimes persisting for days, with freedom following change in environment or elimination of the odor and exacerbation with re-exposure. They feel that the syndrome is as clear cut as any in the field of allergy. They point out that specificity occurs; in other words, the patient may have symptoms from one type of odor or several groups of odors, but others cause no difficulty. If such responses are entirely reflex, due to mucosal nonallergic sensitivity, any sharp or acrid smell should cause difficulty, but this is not true. For example, a patient may wheeze when exposed to wood smoke but may tolerate fresh paint with impunity. They also feel that the syndrome is not psychologic in origin because such things are observed both in infants and adults with the first known exposure. Furthermore, in some cases it is possible to demonstrate positive skin tests to the responsible allergen. They give special case reports to support their contention that these are cases of allergy.

During the past year two reviews in the field of respiratory allergy have appeared. The first, by Gottlieb,[45] is a review of the literature on bronchial asthma during the year 1953, the second, by Kaplan, Ehrlich

and Aaronson,[53] a review of the literature on hay fever during 1952. Since these papers are themselves reviews they will not be further discussed here.

ADDITIONAL NOTES ON ACTH AND CORTISONE

Editorially, the *Journal of Allergy*[24] emphasizes the responsibility of the attending physician to be thoroughly familiar with the undesirable side effects of cortisone and corticotrophin. The article stresses particularly the possibility of activation of unsuspected late tuberculosis or peptic ulcer, the dangers of prolonged administration on decalcification of the skeleton to a point where collapse of vertebral bodies and pathologic fractures occur, and also the danger of atrophy of the adrenal cortex. In the latter case, death may result during a period of stress, such as an operation, unless the cortisone treatment is restarted or additional doses are given intramuscularly at the time of stress. After the period of stress the most careful observation is essential, and prompt and vigorous treatment should be instituted at the first signs of circulatory collapse. In addition, the onset of a severe, acute infection may be obscured when cortisone has been given, but if such occurs it is unwise to stop the cortisone abruptly; rather it should be continued while appropriate antibiotic therapy is given. The article concludes with the observation that prolonged treatment with cortisone is warranted only in such severe conditions as intractable asthma and periarteritis nodosa, and that in chronic asthma other medications should be used rather than attempting to get complete control by cortisone alone.

Swift[95] briefly reviews the literature on allergic reactions to ACTH and reports a thirty-five-year-old patient who had received ACTH on several occasions, the last time resulting in an anaphylactoid reaction. At the time of this report the patient received an injection of ACTH. One hour later she felt hot, and giant hives, nausea and vomiting developed. She felt weak and had to lie down, and her voice became husky. These symptoms soon subsided. When she was skin tested she was found to present positive reactions with pork ACTH, beef ACTH and anterior pituitary extract, but negative reactions with pork extract, beef extract, postpituitary extract and pitocin. Passive transfer was carried out on two subjects with identical results obtained in both cases, the results being the same as had been obtained by skin testing the patient.

Hill and Swinburn[51] review the literature on sensitivity to corticotrophin, and point out that increased susceptibility to hypersensitivity seems to be more likely after the corticotrophin has been given for some weeks or when it is given again after an interval of weeks or months. Two types of reactions are seen. In the first, or immediate reaction, the symptoms come on within minutes of intramuscular or intravenous administration producing bronchospasm and angioneurotic edema, itching, urticaria and very rarely anaphylactic shock. In the second, or delayed type, the symptoms come on several hours after the start of therapy. They report the case of an adult, who had received a prolonged course of porcine corticotrophin and subsequently a prolonged course of bovine corticotrophin. Shortly after the first injection of the latter the patient had an acute anaphylactic reaction, characterized by rigor and unconsciousness, with signs of peripheral circulatory failure and cyanosis. He showed temporary recovery but subsequently died. Prausnitz-Küstner passive tranfer tests done with antuitrin, physiological saline and the porcine and bovine corti-

cotrophin showed a positive reaction only with the porcine corticotrophin. The authors therefore conclude that this reaction must be nonspecific as judged by these tests. This patient had also shown an anaphylactic reaction to the previous course of porcine corticotrophin. Neither previous history nor direct scratch skin tests in the patient elicited any hypersensitivity to pork or beef. Necropsy indicated that death was directly due to anaphylactic shock. These last two papers demonstrate that the use of these drugs is not without danger, and therefore they must be used only when there is a specific indication for their use.

Arbesman and Richard[7] discuss prolonged cortisone and hydrocortisone therapy in a total of seventy-five patients. Only sixteen of the patients were under twenty years of age. They carefully controlled the dosage and watched the patients for side effects. Most of the patients were asthmatics but a few had other allergies. They found that some responded best to cortisone, some best to hydrocortisone, in some ACTH was very effective, but they feel that the proper maintenance level of dosage is more important than choice among the drugs. A comparable effective dose of hydrocortisone was approximately two-thirds that of cortisone. They feel that if patients are carefully watched these drugs are safe for prolonged therapy.

IMMUNOLOGY

Three papers have appeared during the past year attempting to throw some light on the effect of cortisone on antibody formation. In the first by Adams[3] the author studied two groups of male students, first an allergic group consisting of seven people, second a nonallergic group consisting of ten people, for the production of antibodies to typhoid and paratyphoid A & B vaccine. The average antibody response of the allergic group was significantly higher than that of the normal group and therefore the author concludes that allergic people possibly have an abnormal response to antibody formation which may at least partially account for their allergic symptoms. This paper takes into account the formation of one form of antibody which is an immune antibody, not an allergic antibody. Although the author gives some evidence from another large series in the literature demonstrating that allergic individuals have a general resistance to infectious disease far above normal and therefore implying that allergic individuals develop immune antibodies more readily than do nonallergic individuals, it is certainly not the general consensus that allergic individuals are more resistant to infection than are nonallergic individuals. This is particularly not true of respiratory infections which seem to be as common or more common in the allergics than in the nonallergics. However, this is one attempt in the direction of finding out in what ways the nonallergics differ from allergics in their antibody responses.

Hayes[18] injected into Swiss mice formalin-killed *salmonella typhosa*, *salmonella typhimurium* and *pseudomonas aeruginosa* antigens some of which had been mixed with cortisone. Subsequently at various times he measured the local antibody (agglutinins) and antibodies in lymph nodes, spleen, liver and serum, and found that cortisone mixed with the bacterial antigen delayed local antibody formation in the loose connective tissues of Swiss mice. The cortisone also produced a great decrease in the phagocytic index. The inhibition of appearance of the cellular agglutinins was believed to be related to the antiphagocytic action of this steroid hormone.

However, whereas local antibody formation was delayed by cortisone, sufficient antigen escaped from the depot to permit homologous agglutinins to be found much sooner in the spleen and serum of the cortisone-treated animals than in the controls. The author postulated that the reversal of sequence of appearance of local and systemic agglutinins is related to the high initial concentration of cortisone in the loose connective tissue and to the phagocytosis-suppressing activity of this hormone.

Newsom and Darrach[69] studied the effect of cortisone acetate on the production of circulating hemolytic antibodies in the mouse. They describe quantitative immunochemical methods which they used to show that in the mouse cortisone acetate suppresses the formation of circulating hemolytic antibodies to sheep erythrocytes. They found that the amount of suppression varied with both the dose of cortisone acetate and of the antigen, and in the experiments demonstrated that a single subcutaneous injection of 2½ mgms of cortisone acetate in both the male and female Swiss mouse would inhibit almost completely the normal production of circulating hemolytic antibody following intravenous or an intraperitoneal injection of 0.1 mls of a 1 per cent suspension of sheep erythrocytes. By varying the conditions of the experiment they showed that if the experiment is rigidly controlled, using a large number of animals and using the same erythrocyte suspension both for preparation of the antigen and for analysis of the antibody that the procedure has useful applications, such as relating the antibody suppressive activity of different steroids on a quantitive basis. They feel also that the method when adequately controlled also lends itself to a study of possible cortisone antagonists since a rise of antibody levels in animals receiving both cortisone and such antagonists would be significant. This paper is important since it is another paper of this series demonstrating that cortisone acetate can inhibit the production of antibodies in the experimental animal. This is of great practical importance to allergists, since a great many patients are now receiving cortisone to suppress their allergic symptoms, and at the same time are receiving hyposensitizing injections. If the results of this experiment and other experiments on animals can be carried over to the human, it would appear that there is danger of suppressing the immune antibody response and therefore of not producing a satisfactory result with the hyposensitizing injections when cortisone is being given at the same time. Since many patients receiving both methods of therapy seem to respond to the hyposensitizing injections, it is not yet possible to answer the question of whether cortisone is harming this process or not. A great deal more experimental work is required before this answer will be given for the human being who is being treated for allergy.

PROPHYLAXIS OF ALLERGY

Glaser and Johnstone[42] discuss the prophylaxis of allergic disease in the newborn on the basis that a physiologic immunologic immaturity exists in the early months of life that results in sensitization and clinical symptoms caused by the absorption from the intestinal tract of unaltered proteins in potentially allergic children. The authors made a study to determine whether or not it was possible to prevent the onset of allergic disease. For this purpose they studied three groups of children. The first or experimental group consisted of ninety-six infants who were all either offspring or siblings of one or more persons

with one or more allergic diseases. Cow's milk was withheld from each infant from the day of birth. Eighty-eight were given soybean milk, three were exclusively breast fed and five were given meat base formulas. Cow's milk was introduced into the formula from under one month of age up to over nine months of age, most of them receiving it from six to nine months of age. Their allergic histories were reviewed up to the time of writing for the incidence of allergic disorders previous to and after introduction of cow's milk into the diet. The follow-up period varied from seven months to ten years, most of them from two to five years. As a control group the histories of seventy siblings of infants in the experimental group were reviewed for the same data. Only sixty-five were included in the control group, the other five could not be followed long enough. The second control group of 175 subjects was chosen from the histories of 4,710 children in 1,215 allergic families. These children were followed for the same number of years as a counterpart to the experimental group and had the same number of younger siblings with similar allergic histories. Their parents also had allergic histories closely resembling those of the parents of the children in the experimental group. The results of this study showed that the incidence of major allergy was 15 per cent in the experimental group compared with 64 per cent of the sibling control group and 52 per cent of the non-related control group followed to comparable ages. In other words, approximately four times as many infants in each of the two control groups had major allergic disease as in the experimental group. The authors find this statistically significant. From this the authors conclude that in the potentially allergic infant allergic disease can be prevented in many cases by substituting soy bean milk or the meat base formula for cow's milk, withholding cow's milk until approximately six months of age, by which time the period of physiologic immunologic immaturity has largely passed. Editorially[25] the *Journal of Allergy* comments on this paper and criticizes it saying that the data as presented do not form a reliable basis for the conclusions reached. In the first place, the editorial objects to the manner in which the experimental group and controls were chosen. The time over which the ninety-six infants in the experimental group were selected is not stated and it is no more than very questionably implied that these infants were to be subjects of a controlled study at the time they were selected. It is also not stated how the sixty-five infants in the sibling group were selected as controls, and it seems reasonable that this group of controls was heavily weighted with children who were brought to the author's attention because they already had allergic disease. They also do not feel that the second or nonrelated control group was selected in such a way that a truly random sample was obtained. Furthermore, the two control groups appear to have been selected from infants and children many of whom had or may have had allergic disease, and these the authors compare with a group of children who at the time they were selected before or immediately after birth could have exhibited no allergic manifestations. In other words, the experimental group and the two control groups are statistically not comparable. The editorial continues that the criteria for selection of subjects for the experiment, whichever group they fall into, must be set up before selection is made and then rigidly adhered to. Their second criticism is that the authors overlook an aspect of their data which contradicts one of their own conclusions. Among those who developed major allergies the avoidance of cow's milk in the diet during infancy did not prevent the later appearance of sensitivity to cow's milk.

Roughly 50 per cent of those developing major allergies in each of the three groups, experimental and controls, developed allergy to cow's milk. They believe that this is evidence against the concept of immunologic immaturity as a temporary phenomenon associated with the first year or two of life. The authors of the editorial feel the entire question remains open and the answer will require an experiment planned well in advance with all precautions taken to avoid that enemy of science, human bias.

Glaser and Johnstone[41] reply to this criticism in another article. They point out the observations have been made over twenty years and it was the hope during all this time that it would be possible to prevent such manifestations as eczema in the newborn infant. They feel that one evidence of the success of the procedure is the number of new patients who have come to the office for this care because of success in patients known to them. They next point out that it is impossible to conduct a study along absolutely theoretical statistical standards, because in our form of society one cannot pick patients according to such statistical methods, inasmuch as there is freedom of choice on the part of the parent whether the infant will be treated or not. They also point out that they did follow these infants from a period of three months to ten years, the large group having been followed from two to five years. They next describe in detail the method of picking the controls and point out they picked the two groups of controls to give the experiment greater validity, and in as far as possible they picked them without trying to direct the study in order to show a definite conclusion. They answer the criticism that many of the infants later develop allergy to cow's milk, by pointing out that they did not at any time state that the omission of cow's milk from the diet of the newborn infant would permanently prevent the development of allergy to cow's milk and no one would reasonably expect this. They defend the use of the term immunologic immaturity on the basis of observations that many infants who cannot tolerate egg at three months of age can tolerate this food when given it at nine months of age. They feel that this indicates that the infant has matured in this regard as to tolerance for a specific food, and they think that it is reasonable that this should apply to cow's milk. In answer to the criticism that just because cow's milk is withheld in early infancy one would not expect that this would have any influence upon the development of subsequent allergy, they point out this was not a finding which they expected before they started with the experiment, but since it was observed in the experiment there is no reason why it cannot be considered a valid conclusion. To the best of their ability they did not allow prejudice to influence them in the selection of the nonrelated control group, and they do not feel that chance of prejudice was enough to be misleading. They feel that the final judgment will come when others check their work.

This work by Glaser and Johnstone, although it does not give the final answer on this subject, has done a great deal of good since it has caused a lot of discussion and thought on the subject of prophylaxis of allergy in the newborn infant, which in these days of preventive medicine is of very great importance.

Glaser[39] reviews the history and the methods of prophylaxis of allergic disease in the newborn infant and reviews the literature on this subject. He discusses the hereditary aspects of allergy, congenital sensitivity, sensitization *in utero,* recommended diets for the pregnant and nursing mother and the potentially allergic infant, allergy to cow's milk and egg in the newborn infant, the use of soybean milk, and makes some more obser-

vations on his use of soybean milk from the time of birth in the potentially allergic infant. He also discusses sensitization as a result of overindulgence in specific foods, sensitization acquired following gastrointestinal disturbances, environmental correction, immunization of allergic children and the training of allergic children for eventual self-support.

GASTROINTESTINAL ALLERGY

Collins-Williams and Ebbs[19] report on the use of protein skin tests in the celiac syndrome. They discuss a group of celiac patients that had been found to be improved by removing gluten from the diet. The purpose of the study was to determine the correlation between skin tests and clinical experience following the removal of gluten from the diet. Twenty-eight such cases were skin tested with forty-seven of the common foods, including all the cereals, and with the wheat protein fractions, namely gliaden, globulin, glutenin and proteose. Tests were done by the intracutaneous method. In the twenty-eight cases, positive reactions were obtained with many foods but only on six occasions with wheat itself. With the wheat fractions, positive reactions were obtained with globulin three times, glutenin twice and proteose once. Of the total of twenty-eight cases, twenty-two gave positive reactions with one or more foods and ten gave positive reactions with wheat or one of the wheat fractions. These tests therefore show very little correlation between the tests and clinical results. While the wheat gave positive reactions as often as any other food with the exception of egg, it gave this reaction in only six of twenty-eight cases and wheat fractions gave positive reactions in four additional cases. Thus only ten cases gave positive reaction to wheat or its fractions, while eighteen gave negative reactions. The authors feel that although the incidence of positive wheat reactions is much higher than one would expect in a nonallergic group of children, this correlation is far too low to make skin testing worth while as a routine procedure in these cases. Actually there is no proof that these celiac patients who respond to the removal of gluten from the diet fall into the allergic group of celiac syndrome, but this is a real possibility. The authors also review the literature on the allergic aspects of celiac disease, emphasizing those cases which have been described as due to wheat sensitivity.

Ruffin et al[81] report one adult with typical sprue syndrome in whom there was a complete remission both clinically and radiologically on a wheat-free diet, and add that they have treated two additional patients with sprue syndrome who responded dramatically to a wheat-free diet. This paper is of interest because of the similar response which has been shown in certain children with celiac syndrome on a wheat-free diet and the similarity between the sprue of adults and celiac syndrome of children.

Rowe and Rowe[80] review their studies during the past sixteen years on chronic ulcerative colitis and regional enteritis. Their studies in therapy increasingly indicate that atopic allergy to foods and/or pollens, and rarely to drugs, is responsible for chronic ulcerative colitis and regional enteritis. They outline the evidence favoring allergy as a causation of these syndromes. They found that when allergy is the sole cause antiallergic therapy alone controls the symptoms. When secondary infection and avitaminosis are present, their control is also required. They review the histories and studies of 138 cases of ulcerative colitis, most of whom were adults. Results indicated that food allergy was causative alone in 45 per cent, pollen allergy alone in 3 per cent, indicated or questionable

food and pollen allergy in an additional 25 per cent for foods and 18 per cent for pollens. Treatment and study consisted largely of the use of the fruit-free elimination diet plus rice. Other dietary measures of the disease are outlined. All the pollen allergies require prolonged desensitization with multiple pollens and, at times, pollen filters and environmental control. Skin tests at times were negative. With antiallergic therapy with or without adjunctive treatment, excellent results were obatined in 45 per cent and good results in 8 per cent, with excellent cooperation, and excellent results in 2 per cent and good results in 24 per cent, with good cooperation. In the past eight years of the study there were no deaths in comparison with nine in the previous eight years. In the past eight years only two ileostomies and colectomies had been done in cooperating patients. Exacerbations were also fewer in patients. Similar studies on regional enteritis indicated the same causes as for ulcerative colitis. Two cases in which food allergy was indicated as the sole cause are summarized.

Two reviews in this field have appeared in the past year. The first by Collins-Williams[18] reviews the literature on gastrointestinal allergy in infancy. The second by Rowe[79] reviews the subject of food allergy and deals mostly with Rowe's elimination diets and their use.

PENICILLIN SENSITIVITY

During the past year there has been a considerable increase in papers on penicillin sensitivity, as has been emphasized editorially in the *Lancet*,[28] which points out that reactions to penicillin are becoming more frequent and, whereas only two deaths from penicillin had been reported up to 1952, in the next eighteen months published reports amounted to fifteen. Editorially, the *New England Journal of Medicine*[27] also comments on this subject referring to a survey which Welch and his co-workers of the Food and Drug Administration undertook in eleven large cities widely scattered throughout the United States. They surveyed a total of ninety-five large general hospitals with a capacity of 51,000 beds, representing approximately 2 per cent of the general hospitals and about 7.5 per cent of the bed capacity of such hospitals in this country. They discovered a total of sixty-three anaphylactoid reactions, twenty of them fatal, none of which had been previously reported. These reactions were classified as follows: fifty-five from injections of procaine penicillin, one from an injection of penethamate (Neo-Penil®), two from injections of penicillin-O, one from tablets of Bicillin,® three from streptomycin given intrathecally, and one from an injection of streptomycin. Of the twenty deaths, eighteen resulted from the injection of procaine penicillin, one from oral tablets of penicillin and one from intrathecal administration of streptomycin. In addition, twenty-five cases of reported anaphylactoid reactions to penethamate were investigated, raising the total to eighty-eight patients with twenty-five deaths. Previous evidence of sensitivity to penicillin was elicited in twelve cases and the history of bronchial asthma, hay fever and other allergies in twenty-six. This paper stresses how common are anaphylactoid reactions to penicillin, much more common than one would judge from the review of the literature, since none of these have been previously reported and many presumably would not have been reported at all if this survey had not been carried out. Editorially, the ANNALS OF ALLERGY[26] also comments on this same subject.

Collins-Williams and Vincent[21] review the incidence of penicillin sensitivity as reported in the literature, list the forms that penicillin reactions

may take, and discuss briefly fourteen fatal cases which have been reported. They next discuss the factors which influence the development of sensitization to penicillin and briefly review the literature on skin testing with penicillin. They found from their clinical observations that penicillin sensitivity in children is quite rare but is fairly common in adults. They report skin tests done with penicillin on 200 children, two-thirds of whom were nonallergic and one-third of whom were allergic, and found there was no correlation between clinical reactions and skin testing. They discuss the prevention of penicillin sensitivity reactions, the treatment of acute anaphylactic shock due to penicillin and the treatment of other penicillin sensitivity reactions.

Sterling[91] reports nine patients with bronchial asthma all of whom suffered shock reactions, three of them almost fatal, following the use of intramuscular penicillin. All had noted some symptoms after one or two preceding injections of penicillin but did not consider them severe enough to mention. The author describes five cardinal symptoms any one of which, in addition to aggravation of existing chest conditions, is a cause for refusing further parenteral penicillin therapy: (1) syncope, mild or severe, at the time of the injection, or a feeling of faintness recurring periodically for the following three or four hours; (2) a sensation of burning or heat throughout the body especially in the throat, palms of the hand, soles of the feet; (3) local or generalized pruritus never before present may occur in various parts of the body, beginning within a few hours after the injection; (4) a choking sensation in the throat with increasing cough, dyspnea and wheezing; and (5) severe paroxysmal pain varying in location, such as precordial, epigastric or diaphragmatic. Skin tests proved to be not reliable. There were ten patients who gave false positive skin reactions where there was no reaction after injection of penicillin, but the author did not observe negative skin tests which were followed by reactions to subsequent injections. Fifteen patients who experienced one or more cardinal symptoms were refused further injections of penicillin. Trial injections were made in three suspicious cases to determine whether this was justified, and three anaphylactic shock reactions occurred. He also discusses the emergency treatment of shock to penicillin. Because of the dangers of penicillin reactions, he is opposed to the long-acting penicillins.

Roberts[74] reports three workers who, while working in a plant engaged in the manufacture of penicillin, became sensitive to the drug. All patients were severely allergic and would have had to discontinue their jobs had treatment not been successful. All of them showed positive scratch tests to penicillin. The author then desensitized them, starting with very small doses of penicillin and working up to large doses, finally continuing on maintenance doses, and was successful in hyposensitizing all three patients to the extent that they could return to work and were free of any sensitivity reaction after a several months follow-up period. In addition, scratch tests to penicillin became negative in all three cases. The author describes in detail the concentrations of penicillin used for both scratch tests and hyposensitizing programs. He points out that in hyposensitization one must be very careful, since as little as 24 units of penicillin injected subcutaneously was sufficient to cause both local and systemic reactions in one highly sensitive patient. This paper shows conclusively that it is possible to hyposensitize a patient to penicillin so that he can subsequently tolerate large doses. In this case the subsequent dosages were by inhalation in the penicillin manufacturing plant, but it seems quite

practical that this method for hyposensitization could be applied clinically to patients who have shown sensitivity reactions by injection. Particularly in the case of patients with major allergies it would seem worthwhile to attempt this procedure in the hope that they can tolerate penicillin by injection for subsequent infections.

Farmer[31] performed scratch and intracutaneous tests with penicillin on one hundred subjects with no history of penicillin sensitivity, and no positive reactions were obtained. Then the tests were performed on twenty-eight subjects which had shown sensitivity reactions to penicillin. In twelve cases the penicillin reactions were immediate or accelerated, and came on within forty-eight hours. Four reacted to the scratch test and one to the intracutaneous test, so that, in all, five gave positive reactions and seven gave negative reactions. There were fifteen patients whose symptoms came on after three days, the average time of onset being ten days. Scratch tests were positive in two cases and five others reacted to the intradermal test so that, in all, seven gave positive reactions and eight gave negative reactions. Therefore, of the total of twenty-seven cases there were only twelve who reacted to either scratch or intradermal tests. The patch tests were found to be unreliable. The author therefore concludes that a history of penicillin sensitivity is of much more value than scratch or intracutaneous tests. He tried oral desensitization in two cases but obtained tolerance only up to about 5,000 units and this did not seem to last. He found antihistaminic drugs of very little help but found ACTH and cortisone to be quite beneficial in the treatment of penicillin reactions.

Kern and Wimberley[55] have written an excellent review on penicillin reactions and in it include reports on two anaphylactic deaths which had not been previously reported. This review is very complete and includes sixty-one references.

Davis[22] reports five cases all of whom had penicillin reactions manifested as rashes which did not respond to the usual methods of therapy such as antihistamines, epinephrine and ephedrine, but all responded promptly to intramuscular cortisone. In three cases only one injection of 50 mgms of cortisone was necessary for a complete remission of symptoms, but in two cases the dose had to be repeated in twenty-four hours. Symptomatic response occurred in five to eight hours and the time required for recovery was twenty-four to forty-eight hours.

Bell et al[12] report experiments on cats who were given intramuscular and/or deliberate intravenous injections of aqueous suspensions of procaine penicillin. Fifty-one intramuscular injections were given to ten cats without producing any unusual reactions. Intravenous injections, however, produced reactions varying from relatively mild ones to death. Autopsy of the animals who died usually revealed pulmonary embolism. They report a further case of death in a human but at autopsy no anatomic cause of death was found. The authors then review severe and mild reactions to penicillin in humans. They have seven reports in all and feel that these reports of reactions to penicillin in humans parallel the reactions to intravenous injections in their experiments on cats, ranging from death to transitory disturbances without loss of consciousness. They feel therefore that so-called anaphylactic reactions to penicillin which have been reported in humans are due to inadvertent intravenous administration rather than a sensitivity phenomenon. However, in their fatal case which they report, they do not succeed in demonstrating that it was death due to an intravenous injection rather than anaphylaxis. They describe a

technique which they consider safe for administering penicillin which will guard against intravenous injection.

This paper brings up an interesting problem that some of the reported cases of anaphylaxis or reactions to penicillin are due to intravenous injection of the drug rather than sensitivity phenomenon. However, the autopsy findings in humans and those of cats are not parallel, because the cats who died from the injections suffered from pulmonary embolism which is not the usual finding at autopsy of humans who die from penicillin reactions. However, this does not disprove their contention that some of the reactions in the human are due to intravenous injections. The question cannot be settled, but from other observations which have been made on humans it is certain that a great many of these deaths have been true anaphylaxis.

DeBold and Fox[23] report sensitivity reactions to intravenous procaine. These are of interest here because of the fact that penicillin is so frequently given in combination with procaine. They used intravenous procaine for the treatment of arthritis and report a total of over 1600 procaine injections given to 300 patients. In this series there were three reactions to procaine, no other patients having been found sensitive to the drug. One reaction occurred in a patient who was suffering from acute asthma and the procaine caused severe wheezing. The other patients had no personal or family history of allergy. One suffered nausea and shortness of breath with a tremor involving the entire body. The other suffered severe shortness of breath, became flushed, the respirations were labored and the pulse rapid. All of these patients recovered.

Mitchell[66] reports a twenty-year-old male who received intramuscular dicrysticin followed by an urticarial-angioneurotic edema type of reaction which responded to treatment with antihistamines and cortisone. Eleven days after discharge from the hospital he received an inoculation of typhoid-paratyphoid vaccine, tetanus toxoid and diphtheria toxoid, and the next day there was itching and erythema of the palms, soles, and trunk, pain and stiffness in the hands, fingers, and knees, and generalized colicky abdominal pain. With treatment the symptoms subsided in three days. Clinically, this reaction following the injection of the TABTD closely resembled the reaction following the injection of penicillin. Although the author can put forward no explanation for this, since it does not appear that there is any chemical substance in common to both dicrysticin and TABTD, he concludes that this form of inoculation should not be employed shortly after a severe sensitivity reaction to penicillin.

Rosen[77] points out the possibility that penicillin may be present in the daily milk supply. He claims there are definite indications that there is a residual amount of penicillin remaining in milk after penicillin udder therapy by veterinarians, and that this may cause some of the reactions in patients who show clinical allergy to milk. He points out that the amount of penicillin in milk varies greatly from time to time and that pasteurization does not seem to destroy the antigenicity of penicillin. While this is a theoretical possibility for a method of exposure to penicillin either to cause sensitivity or to produce reactions, it is unlikely that the concentration would ever be great enough to cause any symptoms or to produce sensitivity.

Carter and Cope[17] report a nonfatal anaphylactic shock reaction after the application of penicillin ophthalmic ointment and claim this is the first case so reported. Four additional cases of fatal anaphylactic shock to

penicillin have been reported by Fisher,[32] Etter and Merryman,[30] Altounyan,[6] and Bell.[11]

Rosenthal[78] reported eight fatal anaphylactic reactions to penicillin, all found in an investigation of sudden deaths conducted by the Office of the Chief Medical Examiner of the City of New York. Seven of the cases were adults, one an infant. Autopsies were performed on six.

This brief review emphasizes the importance that penicillin reactions are now playing in the practice of medicine. Up to the present time there have been fifty-five anaphylactic deaths due to penicillin reported in the literature, fifty-two in adults and three in children. However, this is not the true picture. In addition the authors know of four other cases, one in an adult in Toronto, one in a child in Winnipeg, one in a child in Chicago, and one in a child in New York City, the latter two of which were reported by Dr. Matheson at the Chicago meeting of the American Academy of Pediatrics in 1954. This brings the total to fifty-nine, and there are undoubtedly many more which have never found their way into the literature. In addition, there are other forms of death from penicillin, such as exfoliative dermatitis and generalized vascular reactions, and also more numerous severe reactions and disabling illnesses which do not result in death. Therefore, the problem for the practicing physician is very great indeed, and this is especially true for those who care for allergic individuals. No patient suffering from a major allergy should ever be given penicillin if any other medication could be used, and this should apply also to nonallergic individuals. If possible, the drug should be given by the oral route if it must be used, and intramuscular therapy used only in the severely ill patients who cannot take it by mouth. However, it is preferable to use other antibiotics if possible, reserving the all important penicillin for very severe illnesses where injection therapy is essential.

ALLERGY TO DRUGS OTHER THAN PENICILLIN

Herrell[49] gives a general discussion of toxicity and allergic reactions to penicillin, streptomycin, chloramphenicol, aureomycin, terramycin, erythromycin, neomycin, bacitracin and polymyxin and also discusses the management of these reactions.

Lane et al[58] in a discussion of unusual toxic reactions to sulfonamide and antibiotic therapy review the literature from 1936 to the first of November, 1950, on the unusual manifestations of toxicity which have been described in case reports, dealing specifically with toxic reactions observed after and during systemic administration of the following antibacterial agents: aureomycin, bacitracin, chloramphenicol, dihydrostreptomycin, penicillin, streptomycin, sulfadiazine, sulfaguanidine, sulfamerazine, sulfanilamide, sulfapyridine, Sulfasuxidine,® sulfathiazole, terramycin and tyrothricin (applied topically).

The literature on aureomycin, chloramphenicol, neomycin and terramycin from November 1, 1950 to January 1, 1953, is also reviewed. In table form they summarize over 700 individual case reports showing the toxic reactions which have been described and giving the reference or references for those toxic reactions. Other than listing these toxic reactions and the references for them the authors do not discuss the papers and do not give any conclusions about these reactions. Since this paper with nearly 800 references is a very handy and convenient means of finding references to any toxic reactions which have been reported for any of the drugs listed, it is a very useful one.

Kutscher et al[57] in table form review all of the available literature up to January 1, 1953, involving clinical toxicity to Aureomycin® Chloromycetin,® penicillin. streptomycin, dihydrostreptomycin, sulfadiazine, sulfaguanidine, sulfamerazine, sulfanilamide, sulfapyridine, Sulfasuxidine,® sulfathiazole, Terramycin,® bacitracin, elkosin, Gantrisin® Ilotycin,® Magnamycin,® neomycin and polymixin B. This includes a bibliography and is an excellent source of reference for anyone interested in the toxic manifestations of any particular drug.

Kutscher et al[56] report a well controlled study in which Bacitracin troches were administered to 100 patients, Tyrothricin troches to 100 patients, Gramicidin troches to fifty patients and Polymixin B-Bacitracin troches to 100 patients and the resulting side reactions evaluated. In all cases there was a control series of patients who received placebos. Approximately 10 per cent of the patients in each group showed reactions but the reactions which occurred were of the mildest degree, with one exception, and did not require cessation of medication. They did not particularly effect the oral, pharyngeal, rectal or anal areas. When these were compared with the results of previous studies with Terramycin® Aureomycin,® and procaine penicillin G troches, the percentage of patients showing reactions, the average number of reactions per patient, and the average number of reactions per reactor were appreciably lower with the four drugs under study in this paper. The authors point out that their results refer only to the concentrations of drugs in the troches under use and that if these concentrations were increased there might be more reactions. The reactions that were observed were confined almost entirely to the gastrointestinal tract and were quite mild in nature. No delayed gastrointestinal reactions were reported. The authors feel that the instances of mild gastrointestinal complaints in the placebo groups indicate that some of the reactions observed result from the taste-masking bases in the troches in which the antibiotics are incorporated.

Berkowitz, Glaser and Johnstone,[13] in an effort to determine the frequency of usage of various common medications as well as the incidence of adverse reactions to them in pediatric practice, prepared a questionnaire for 500 children chosen at random from a pediatric outpatient clinic and a private practice and in each case listed the drugs which had been given to the children as well as adverse reactions to them. The adverse reactions were divided into definite allergic reactions and side reactions which may or may not have been allergic. The study included 500 infants and children ranging in age from two months to fifteen years. The drugs most commonly used were aspirin, penicillin. sulfonamides, phenobarbital, codeine, Aureomycin,® Pyribenzamine® in that order of decreasing frequency, and in all a total of twenty drugs were listed. It was found that both allergic and side reactions were much more common in the allergic group of children, the study being divided into 332 allergic children and 168 nonallergic children. In the allergic group 20 per cent gave allergic reactions to these drugs and in the nonallergic children only 2.4 per cent showed allergic reactions. Similarly with the side reactions in the allergic group there were 36 per cent, and in the nonallergic group only 3.5 per cent, who showed side reactions. In the total group 12.8 per cent showed allergic reactions and 25 per cent side reactions. This study indicates a very definitely higher incidence of drug reactions in allergic as compared with nonallergic children.

Macaulay[60] reports nine patients who were being treated for allergic

rhinitis or hay fever. In all cases the antihistamine therapy produced relief of their symptoms but coincidentally there was the appearance of asthma. In most cases the effect was reversible and cessation of the therapy allowed the hay fever or allergic rhinitis symptoms to return with disappearance of the asthma. He points out that this has been reported several times previously.

PSYCHOLOGICAL ASPECTS OF ALLERGY

Abramson[1] evaluates the theory of maternal rejection in allergy and presents a point of view that the psychodynamic theory of maternal rejection, so often cited as the basic part of the emotional difficulty of the patient, is often not only incomplete but may frequently be misleading in understanding and treating the allergic responses of children and adults. He holds that the allergic child is not primarily rejected by the mother or father but that rather the opposite may occur. For example, in certain cases where the eczema persists and no simple allergic process can be discovered or where the intensity of the asthma progresses in uncontrollable form, the disturbance in the parent-child relationship is not parental rejection but rather mutual engulfment (introjection). In other words, he does not feel that the notion of rejection provides the physician with sufficient therapeutic material for the rapid development of insight into the parents and the patients, whereas the notion of engulfment is more successful in explaining to parents and patients the nature of the difficulty and practical ways of solving them. In support of this thesis he reports several cases both in children and in adults, including verbatim recordings of the analysis of these patients, and from the study concludes that although treatment of the allergic patient should begin with study of his allergic hypersensitiveness from the point of view of specific antigens it should not end there. Especially where the therapeutic results are unsuccessful the study should be continued by instruction of the patient in other matters. He should be instructed to look for personal sensitiveness, that is, to emotional tensions within himself in response to people. While giving psychotherapy the physician should bear in mind that the allergic individual may either have had a childhood in which parental domination and engulfment prevented his growth of independence or where in adult life his dependency upon a demanding engulfing parent has not been replaced by mature relationships. Parental rejection may occur when the parent becomes enraged at the failure to form the character of the allergic child in a pattern based upon the parent's own narcissistic needs.

Mitchell et al[65] studied the emotional aspects of pediatric allergy in a group of twenty-two children with dermal and/or respiratory allergy. These patients were investigated and treated with the usual allergic methods but were also studied quite extensively from the emotional point of view. It was felt that the mothers were relatively and absolutely rather strong, active and anxious, with great need to be in control, but that in comparison the fathers were psychologically weak. The position of the child in the family was rather special and these children occupied roles of particular importance to the mothers. There was periodic oscillation of the mother's attitude toward the child exchanging from extreme concern and overprotection to an attitude of intolerance and impatient annoyance. The children of both sexes showed much stronger identification with the mother than with the father. The children showed great

ungratified dependency needs and at the same time unconsciously portrayed their parents and their family members as equally frustrated persons from whom they could expect and receive little gratification. The authors believe that the allergist or pediatrician is in a much more advantageous position to supply the emotional support and insight in therapy for these patients, and that it is only exceptional cases which need handling by the psychiatric specialist. The authors make no claim that emotional factors are the cause of the allergic manifestations, but rather that emotional factors must be considered in all of these patients in addition to the usual allergic therapy.

Friend and Pollak[35] point out that in therapy of the allergic child there are many factors to be considered other than the direct relationship between the child and the therapist, for example very careful preparation of the family, particularly the mother, in order to secure an effective therapeutic situation for the direct treatment of the child, and it is also necessary to obtain co-operation from the father with the attending physician. They give a long case report to illustrate the complexities of these relationships showing how they may take up more time than the actual therapy of the child himself.

Kaufman[54] discusses the psychosomatic aspects of food allergy. He discusses some highly specialized problems of idiosyncrasy to foods and discusses the interplay of allergenic and psychogenic factors in the production of patients' food-induced ill health. He points out that reactions to food may be caused in some cases by psychogenic mechanisms, by allergenic mechanisms, or both, and that the relative importance of the various factors in the production and continuance of food-induced illness must be estimated correctly in order to plan a correct program of therapy. The paper is based on experience in the treatment of approximately 600 patients who have been seen with certain food-induced syndromes. Allergic reactions following the ingestion of offending foods have certain characteristics. There is a latent period between the ingestion of the food and the appearance of signs and symptoms. There is a certain pattern of development and regression of signs and symptoms. They have intensity and duration. These properties in part determine the nature of allergic reactions to repeated ingestion of subthreshold and threshold doses of offending foods. Each primary allergic reaction set off by ingestion of an unknown allergenic food starts off a pattern of behavior which becomes an important part of the patient's reaction to the offending food. Not knowing when he will be well or sick acts as a frustrating cue in response to which a patient develops a human counterpart of the non-problem-solving behavior described for frustrated rats. This secondary reaction pattern of behavior often becomes so prominent and extensive a part of the patient's complaints to the doctor that even an astute allergist at first glance may consider mistakenly that the patient's problems are purely psychiatric. A further careful clinical study of such a patient will show that he has experienced primary allergic reactions to an offending food which in turn sets off a chain of behavior patterns which are the patient's unconscious response to his allergic illness. Sometimes a secondary behavior pattern engendered by intermittent allergic episodes may become so incapacitating to the patient that they constitute his chief health problem. The author concludes that the best management of all patients with food allergy requires both expert allergic therapy and expert psychotherapy.

MISCELLANEOUS

Small and Small[86,87] have written two papers on the treatment of rheumatic diseases by desensitization with an aqueous extract of streptococci. The first describes the use of this product in rheumatic fever, chorea and rheumatic carditis. They discuss a method of desensitizing patients with these diseases with an aqueous extract of streptococcus cardioarthritidis. This is used in very small doses which the authors describe in detail and the patients are desensitized in essentially the same manner as one desensitizes for other allergies like asthma and hay fever. They emphasize that the dose must be kept very small. They describe three patients who were treated by this method. The second paper describes the same technique for rheumatoid arthritis. They now have fifty-one patients who have been under treatment for more than two years; the average period of treatment for each of the fifty-one patients is 10.2 years. They feel that this is a satisfactory method of reversing the course of rheumatoid arthritis and controlling it over long periods of time with a minimal amount of treatment, but stress that basic general management in the treatment is also necessary.

While this form of therapy appears rational, inasmuch as most people who work with these diseases believe that they are hypersensitivity reactions, it is obvious that such a method of therapy is very, very difficult to assess. Many patients with these diseases do very well with the conventional methods of treatment, and therefore when one uses a desensitization procedure at the same time it is very difficult to assess how much of the improvement is due to the desensitization procedure and how much is due to the other methods of treatment. Only if this were done on a very large controlled series would one be able to come to any conclusion as to whether this is a logical method of treating these patients.

Leney[59] reports four children suffering from either petit mal and/or grand mal epilepsy in all of whom the epilepsy was due to allergy, in some cases to foods and in other cases to inhalants and pollens. In all of them the symptoms were brought under control by antiallergic therapy. He concludes that patients with so-called idiopathic epilepsy who have a personal or family history of allergy should be thoroughly studied from the allergic standpoint especially if other treatment has failed.

Halpin[46] reports a man who, following a puncture wound, was given 15,000 units of antitetanus serum and 300,000 units of penicillin. Twenty days after the injection a Bell's palsy appeared, and he was started on treatment with oral cortisone. There was some improvement within four days and nine days after cortisone administration he was practically normal in appearance. Because of the time element following the injections the author feels that it is highly suggstive that the Bell's palsy was a sensitivity reaction either to the serum or the penicillin, although it is impossible to tell which. This reaction is probably placed in the domain of neurological sequelae of serum sickness. It results from a peripheral edema which is usually self-limited.

Garvey[37] reports twenty cases of neuritis observed following the administration of tetanus antitoxin. The patients complained of very severe pain and the author points out that neuritis should be suspected in serum sickness if severe localized or radicular pain appears early in the course. However, the pain is usually so severe that the detection of

paralysis is difficult. Paralysis is flaccid in type. In two cases there were associated cerebral manifestations.

Mark[62] briefly reviews the literature on climate as it influences childhood allergy and emphasizes the literature on the effect of the Florida climate on childhood allergy. He next describes a questionnaire which was sent out to pediatricians and allergists both in Florida and in various parts of the country. The consensus pertaining to south Florida was that if its climate favored improvement it was largely because of the reduced incidence of upper respiratory infections, but that some children sent to Florida because of their allergy do not improve and some children develop new allergies. The author's own opinion from his personal experience is that the child with allergy may benefit from the climate in southeastern Florida if all other means have been exhausted in the former place of residence, but he does not believe that it is a place for a trial and error method of therapy. Furthermore the physician who sends the child to the new area should be fully aware of the conditions in that area as to whether they will give relief from the particular allergens from which the patient is suffering. In other words, every child must be managed on an individual basis and not simply be sent to a new climate in the hope that it will help him.

This subject is also discussed editorially in *The Journal of the American Medical Association*.[29] The editorial points out that it is very common for physicians to recommend a change of climate for a patient who is not showing adequate response to therapy. This causes a great deal of psychologic and financial distress to many families who are so ill-advised and also puts a great deal of stress on the communities to which they move, partly because there is not sufficient work for these people and also because they become wards of the state. The editorial urges that physicians think the subject over carefully before they give such advice to a particular patient, and determine whether it is actually necessary for the patient to move or whether with improved methods of treatment he could not be better treated at home.

Mueller and Hill[67] review the literature on allergic reactions to bee and wasp stings, and describe the methods of identification of the various kinds of insects in this class. They then discuss the immunology of bee and wasp stings, pointing out that the question is not answered as to whether or not there are cross reactions between the different kinds of insect bites. They also point out that it is not clearly established whether atopic individuals are more susceptible to the insect bites than the nonatopic individuals. They discuss desensitization with extracts of these insects and highly recommend them, since this procedure can often be a lifesaving measure by preventing a patient who has suffered a severe anaphylactic reaction from having a subsequent acute reaction. They report seven cases, all in children, whom they have under treatment at the time of writing the paper. They feel that if the reaction is definitely due to bee sting the best procedure is to use bee extract alone, but if it is not clear what type of insect produced the reaction one should use a mixed extract of bee, paper wasp, hornet and yellow jacket. The question has not been settled as to how long the injections should be continued but they feel that in the present incomplete state of knowledge the inoculations should be continued over a long period of time to be on the safe side. They give a suggested dosage schedule consisting of thirty-two inoculations and point out that great caution is necessary since the patient is apt to

have a severe reaction to the extract. They also give a list of the manufacturers of bee and wasp extracts.

Schenken et al[82] describe a fatal anaphylactic reaction to a bee sting with autopsy findings and report that nine other cases have been reported with autopsy findings. This patient died twenty-five minutes after the sting.

Sobel[88] discusses adenotonsillectomy and its relation to asthma. The author points out that there is considerable confusion among the profession as to the relationship of tonsils and adenoids to bacterial asthma. There are three schools of thought: one that the tonsils and adenoids can act as foci of infection and that if these foci are removed the asthma will be favorably influenced; two, that the adenoids and tonsils play an important role in preventing a spread of infection in the upper respiratory tract to the lower respiratory tract, and the removal of the tonsils and adenoids may precipitate asthma in an allergic individual; and, three that the indications for adenotonsillectomy are the same for allergic and nonallergic patients. In an attempt to clarify this, a total of 100 patients, the vast majority of whom were children, were studied, thirty-two patients who had not had adenotonsillectomy and sixty-eight patients who had had adenotonsillectomy before coming under treatment. In the group of sixty-eight patients who had had their tonsils and adenoids removed forty developed asthma for the first time after the operation and twenty-eight had asthma before the operation. In the forty patients who developed asthma for the first time after the operation, 20 per cent developed their asthma in the first year after operation and a total of 40 per cent developed asthma within two years after the operation. However, the indications for removal of the tonsils and adenoids were predominantly for chronic running nose which had not been proven to be infectious and may have been allergic. In the twenty-eight patients who had had asthma for varying lengths of time before the operation and prior to coming under allergic management, 82 per cent had recurrence of asthma within the first year after removal of the tonsils and adenoids. The reasons for operation were chronic runny nose and to relieve the asthma. It was found that there was approximately the same percentage of mild to moderate and severe asthma in the group with intact tonsils and adenoids as in the group that had had them removed. The author therefore concludes that indications for adenotonsillectomy are the same in allergic and nonallergic individuals, and that the presence or absence of tonsils and adenoids makes no difference in the severity of the asthma. If the operation is indicated after allergic treatment has been started it should be performed during a pollen-free period, because during this period an attack of asthma is more likely to be precipitated.

Hamilton and Bendkowski[47] describe the incidence of allergic disease noted over a period of one year in a general practice comprising about 4,000 patients varying in age from birth to over seventy years. Of these patients they found asthma to be present in 1.7 per cent, urticaria in 1.8 per cent, allergic rhinitis in 0.8 per cent, atopic eczema in 0.7 per cent and drug allergy in 0.3 per cent. While this is an attempt to assess the incidence of allergic disease in general practice it, of course, does not represent the incidence of allergic disease in the general population, which is generally considered to be 10 per cent. However, it does demonstrate that these diseases do occur in sufficient frequency even during a period of one year to make knowledge of their investigation and treatment essential for every general practitioner of medicine.

Becker[10] reports a case of favism in a two-year-old boy, the eighth case to be reported in the American literature. This child was treated with cortisone and showed very rapid improvement.

Owings[70] reports a case of a nine-year-old girl who was to be given gamma globulin because of contact with a case of poliomyelitis. She received her skin test for sensitivity using 1/10 cc of 1:100 dilution of gamma globulin injected intradermally. Within one minute she went into acute anaphylactic shock. She was treated with epinephrine and Benadryl,® and recovered. She had received an antimeasles injection eight years previously but had no other history of contact with human serum. The author therefore recommends that a routine skin test be made on all subjects before the administration of any type of immunization containing human serum.

Mansmann[61] in a study of sensitivity reactions in immunization with influenza virus vaccine reports two series of patients who were immunized with the vaccine. The first group consisted of 150 allergic patients who were not sensitive to chicken, egg or feathers either clinically or by skin test. They were tested intracutaneously with 0.05 cc of the vaccine concentrate. Eleven per cent gave no reactions and were immunized with 1 cc of the vaccine, seventy-one per cent gave local reactions and were immunized with divided doses, eighteen per cent gave a general reaction or a large local reaction and were not given any of the vaccine. The second group consisted of 1,000 individuals who were also allergic, but in this case the patients who gave positive skin tests to chicken, egg or feathers were not excluded from the study unless they gave exceedingly strong reactions with dilute extract. They were tested intradermally with 0.05 cc of a 1:00 dilution of the vaccine, and, if there was no significant reaction later with the same quantity of concentrated vaccine, they were immunized starting off with the 1:100 dilution of vaccine working up the dosage until a total of 1 cc of concentrated vaccine had finally been given to those patients in whom treatment was completed. In some, treatment was discontinued because of large local reactions with the larger doses. The author divides these reactions to the vaccine into three types: (1) reactions due to fowl sensitivity, (2) reactions to the preservative or inactivator chemicals in the vaccine, and (3) delayed reactions, whether local or general, which were the induced type of sensitivity. The author concludes that if persons clinically sensitive to fowl are eliminated, it is safe to give immunizations of 1:100 dilution of the A and B virus vaccine to any patient whether allergic or not, whether adult or child. He recommends the dose to be raised through three dilutions until 1.0 cc of the total vaccine concentrate has been given. The injections are stopped at any level when untoward local or general reactions are observed.

Speer[90] briefly views the history of tension-fatigue syndrome in children and gives some case reports of this condition. He describes these children as those who seem to be torn between two extremes of feeling, one an extreme overactivity or tension, the other unreactivity or fatigue. He reports six cases of quite serious behavior problems in children all of whom were found, sometimes with skin testing and sometimes by elimination diets, to be sensitive to foods and their behavior problems showed dramatic improvement when these foods were removed from their diets. He finds that foods are the most common offenders and are found in approximately this order of frequency: milk, chocolate, egg and corn. The author points out that allergic tension-fatigue merits a place in the differential diagnosis of behavior problems in childhood, but emphasizes

that the differential diagnosis must exhaust a wide variety of psychic and somatic influences before an allergic diagnosis is made.

Glaser[40] reviews the literature on migraine in children and points out that from his own observations the incidence of migraine in the pediatric population of the United States is probably not significantly over 1 per cent. However, it does occur at all age groups even in children and has been observed as early as two weeks of age. The prodromal symptoms are described in detail. These are different from those in adults and are more apt to present a loss of appetite and abdominal discomfort instead of the irritability and abnormal hunger which are so common in the adult. It may also be associated with fever even up to 104 degrees. When these children are seen it is important to rule out errors of refraction or nasal congestion as a cause of headaches. The purpose of this paper is to call attention to the fact that some cases of migraine in childhood are due to food allergy, as has been pointed out by several authors. Most of the children with migraine which the author has seen had been brought in for consultation because of allergic difficulties, and the migraine was elicited only in the course of history taking. In all instances in which the migraine could be proved due to food allergy, the offending foods were known by experience or were discovered by elimination diets, skin tests being useless. Chocolate, wheat, milk and egg were the most frequent offenders. Symptomatic treatment of migraine is discussed.

Butler and Wolman[16] discuss the trends and early feeding of supplementary foods to infants. The article summarizes the results of a questionnaire which was mailed to all physicians throughout the United States whose practice was wholly or predominately pediatric, the purpose of which was to find out the current national habits with respect to giving solid foods to infants. Over 2,000 replies were received and the report tabulates these results. The results provide information on the practice of pediatricians caring for over one half million infants. The survey showed a very early trend to the introduction of solid foods in infants' diets, 13 per cent of pediatricians introducing them to normal infants as early as two weeks and another 30 per cent between two and four weeks. Single grain cereals were prescribed first in 64 per cent, multigrain cereals in 17 per cent, fruits in 11 per cent and so on. The question of approximately how many cases of food sensitivity were treated in 1953 showed the average number to be 26 per doctor. When this average figure was correlated with the number of newborn infants it was found that 10.4 per cent of these infants exhibited some form of what was termed food sensitivity. Twenty-two per cent of physicians felt that there was an increase in the incidence of food sensitivity in the past two years, 72 per cent that there was no increase. Of the foods considered involved in the etiology of food sensitivities, milk was considered responsible for 31 per cent, egg yolk 27 per cent, multigrain cereals 22 per cent. The symptoms which most frequently indicated food sensitivity were skin manifestations in 36 per cent, gastrointestinal symptoms in 55 per cent, rhinitis in 3 per cent, asthma in 1 per cent, others in 0.3 per cent. Therapies used in treating these cases were elimination diets in 45 per cent, modified milk and milk substitutes in 9 per cent, soybean protein in 5 per cent, meat protein in 0.3 per cent.

This article has considerable value, inasmuch as it does show the trend for early feeding of infants and states the ages at which various percentages of pediatricians start solid foods. However, from the point of

view of allergy it does not answer any question satisfactorily. It certainly does not show the incidence of food sensitivity in young infants, because the questionaire gives no room for pointing out how the diagnosis of food sensitivity was made. It is also obviously a recollection of facts by the various pediatricians, because it is difficult to believe that many of them actually went over their records in detail at the time when they answered the questionnaire, as this would have taken a considerable amount of time. It also does not answer in any way the very important question of whether the early introduction of foods into the infant's diet leads to food allergy, and in essence the opinions expressed on this question in the remaining part of the review are personal opinions of the various authors and are not proved by facts found in the questionnaire. However, the paper does leave one with the unescapable conclusion that pediatricians know too little about food allergy.

Goldman and Lau[43] review the literature on acute pericarditis associated with serum sickness and report two patients, both of whom had serum sickness with an increased area of cardiac dullness and a loud pericardial friction rub following an injection of tetanus antitoxin.

Two books of interest to pediatric allergists have appeared during the past year. The first by Swartz[94] is a book on allergy in children prepared for the lay public. Dr. Swartz covers the discussion of allergy in children fairly completely, points out to parents the necessity of treating allergy, treating it early, and treating it thoroughly. This is a very excellent book for parents of allergic children. In an appendix is included the composition of various foodstuffs, the composition of the various strained and junior foods which are on the market, and a list of foods that have been prepared especially for allergic children and where to obtain them. The second by Michal-Smith[64] includes a chapter by Bret Ratner which is a discussion of the allergic child with emphasis on the integration of the psychosomatic and somatic aspects of the chronically ill allergic child. This chapter stresses the need for complete appraisal of the allergic child without concentrating on one small aspect to the exclusion of other aspects.

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(Dr. Collins-Williams)

FOURTH EDITION OF "PROFESSIONAL FILMS" NOW BEING COMPILED

A completely revised fourth edition of "Professional Films" is now being compiled, which will include new sections providing biographical data on authors and information on the audio-visual activities of medical and dental schools and post-graduate teaching centers. Over 28,000 copies of previous editions are now in use in this country and abroad. This audio-visual information is provided to the medical profession by the Academy-International of Medicine in an effort to disseminate professional knowledge. Readers of the ANNALS are urged to help by informing film authors of this announcement so they can write for a questionnaire or by providing the Academy-International of Medicine, 601 Louisiana Street, Lawrence, Kansas, with the film title, full name, and address of any film author.

PHYSICAL ALLERGY

A Review of the Recent Literature 1949-1954

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A review of the literature of the past five years on the subject of physical allergy reveals that our knowledge concerning these physical phenomena has advanced little since Duke's[3] original paper in 1924. It is also striking that so few papers are written concerning this most interesting subject. One wonders why there is such a lack of interest when methods of testing are quite simple and can be conducted quickly and efficiently in any allergist's office. It is of interest also to speculate that many more cases would be seen if the diagnosis of physical allergy was considered and suitable tests performed; that better results might be obtained in many cases of allergy now considered treatment failures if attention were directed toward diagnosis and treatment of physical allergy.

ETIOLOGY AND PATHOGENESIS

There is still much speculation concerning the etiology and pathogenesis of physical allergy. Kierland[18] reviews the five possible mechanisms of action that may explain the various phenomena of physical hypersensitiveness. It is worth repeating them.

The first explanation is that of a primary physical allergy operative on the basis of specific antigen-antibody reaction. The second explanation is basically that of allergy, in which the antigen is autogenous and perhaps is some chemical or physico-chemical alteration of tissue protein. In substantiation of this, Sherman and Seebohm[31] were able to fractionate the serum proteins of a patient with cold hypersensitiveness. The individual fractions were not antigenic by passive transfer technique, but certain mixtures of the fractions were.

The third mechanism is that of a histamine effect due to liberation of histamine-like substance from injured tissue. The fourth possible mechanism of action is that which Urbach designated "cold-specific vasomotor neuropathy" or "cold pathergy," in which an instability of the central or peripheral vasomotor mechanism is assumed to be responsible for the abnormal neurovascular response to physical agents. And, finally, there is Duke's[4] concept in explaining the "reflex-like" reaction in which he assumed a disturbance in the temperature-regulating mechanism in the region of the thalamus.

Williams[34] has written at length to popularize the concept that allergy is due to an autonomic dysfunction and that this is more consistant with clinical practice than the antigen-antibody concept. It is suggested that allergy be defined as "an inherited predisposition to a localized type of autonomic dysfunction mediated by cholinergic fibers of the autonomic system." In these localized areas a stereotyped reaction of the peripheral vascular bed occurs consisting of arteriolar spasm with atonic dilatation of the capillaries and venules. He believes that this picture produced only by a maximal stimulus in a normal individual may occur in certain tissues and organs of an allergic individual in response to a normally minor stimulus; that these reactions result in greater or lesser degrees of cellular

damage and the release of histamine and other toxic substances. Typical allergic edema or necrosis may result and be classified empirically and clinically as allergy.

It is felt that an antigen-antibody reaction may be associated with the vascular reaction and may aid in damaging the cell, but it is a secondary phenomenon, phylogenetically more recent than the vascular component of the autonomic reaction. Since physical allergy has no definite antigen-antibody mechanism, the feeling is that cellular injury and the typical clinical pictures are produced by anoxia and that its normal physiologic prototype can be considered the alarm reaction of Selye.

The properties of acetylcholine are reviewed by Hopkins[12] who attempts to explain the mechanism of physical allergy on the basis of these properties. He reviews the literature and summarizes the following hypotheses suggested to explain the mechanism by which physical stimuli act:

1. Light sensitivity might be explained by the presence of a photodynamic substance without assuming an immunologic mechanism.
2. Proteins or other normal skin constituents might be altered by physical agents and act as allergens.
3. Acetylcholine released by physical stimuli might act as an allergen.
4. One physical agent (cold) may effectuate the reaction of an allergen and antibody already present.

An attempt is made to explain many of the cases in which the lesions are supposedly caused by psychic disturbances on the basis of release of acetylcholine.

Rajka and Asboth[24] demonstrated, by means of a so-called reagin-increasing method, positive Prausnitz-Küstner reactions in all four of their patients who were hypersensitive to cold. In the method used, blood is taken after the patient is exposed to cold, when the serum contains more reagin. By a reagin-fixation method the serum is injected into a site previously cooled with the local application of ice. Positive results are obtained in instances in which the usual passive transfer test has failed.

COLD SENSITIVITY

The literature of the past three decades concerning cold sensitivity is reviewed by Kelly and Wise.[15] The clinical and laboratory findings are correlated in fifty-four reported cases of cold sensitivity appearing in the literature from 1925 to 1951. It was found that there was no definite age or sex distribution, and most patients manifested a local reaction followed by systemic symptoms. Systemic manifestations could be prevented by applying a tourniquet proximal to the chilled part, usually the hand. Although they state that release of the tourniquet is followed immediately by systemic symptoms and signs, Duke found that tourniquets tightly applied around the arms above the elbow did not block systemic reactions nor did release of the tourniquet add particularly to the reaction. Passive transfer tests were found successful in about one half the instances attempted. Eosinophilia was unusual. The treatment of choice was desensitization by repeated exposure. Antihistamines were ineffective in most cases.

They report a case demonstrating an unusual sensitivity of the hands exposed to low environmental temperatures with resulting swelling. This reactivity followed an undiagnosed dermatitis of the hands. They conclude that their case is an example of acquired altered reactivity of the vasculature of the hands, possibly associated with liberation of histamine-

like substances in the tissues. Antihistaminics and intramuscular ACTH failed to alter the response. Intravenous ACTH blocked the reaction temporarily.

Cryoglobulinemia is a term applied to a condition in which the serum contains a cold precipitable protein, and the term cryoglobulin is applied to any one of a group of proteins with the common property of precipitating or gelifying from cooled serum. Barr, Reader and Wheeler[1] describe two cases in whom cold precipitable proteins were demonstrated in the blood and who developed symptoms probably attributable to their presence. The most prominent symptoms attributable to cryoglobulins are sensitivity to cold with Raynaud's syndrome or purpura and a tendency to excessive bleeding from many mucous membranes. Cryoglobulinemia does not appear to be related to the phenomenon of cold auto-isoagglutination, although the clinical manifestations of the two conditions may be similar.

An unusual case of cryoglobulinemia associated with cold urticaria, purpura, and Reynaud's syndrome is reported by Steinhardt and Fisher.[33] They could not accomplish passive transfer in ten donors' skins. ACTH and cortisone produced no appreciable difference in onset, size, and duration of the whealing reaction to cold exposure. The degree of cryoglobulinemia was influenced by hormone therapy in that the precipitable portion of the serum was reduced from 12 to 18 per cent of the total serum volume to approximately 4 per cent. Intravenous Benadryl® caused a reduction in the size and duration of the urticarial wheal upon subsequent exposure to cold. A refractory period of at least seventy-two hours' duration occurred after inducing a wheal by cold exposure. It is postulated that this phenomenon may be due to the exhaustion of antibodies.

Herlitz[11] reports a case of cold urticaria in which, judging from clinical and therapeutic experiments, histamine played a minor role while acetylcholine proved able to evoke the symptoms locally. Furthermore acetylcholine therapy led to a considerable improvement of the patient's condition, after attempts at desensitization with histamine had failed. The sensitization to cold in this case followed a serum sickness produced by a tetanus antitoxin injection. Desensitization experiments with histamine, as well as with horse serum, were unsuccessful. Acetylcholine proved able to evoke local symptoms, and therapy directed to acetylcholine brought about considerable improvement in the patient's condition. The author is of the opinion that the effect of acetylcholine in this case is due to a blocking of the enzymes which normally break down the acetylcholine in the tissues, the blocking effect possibly being exerted directly by the cold. Contradictory reports in the literature concerning the exhaustion of the power to react in cold urticaria are discussed. On the basis of experiments conducted, it is concluded that exhaustion of the cold reaction depends upon the degree of cold applied, a higher temperature apparently causing exhaustion more rapidly than a lower temperature.

Herlitz[10] also reports a case of cold urticaria occurring only after the patient had ingested menthol throat lozenges. Identical urticarial reaction appeared at the contralateral skin site after exposure of one of the arms to cold. The theory is proposed that impulses were transferred to the other arm via a migrating reflex.

Illig[14] conducted studies employing a standardized cold exposure to the skin in which he attempted to prevent urticaria in a cold-sensitive patient by the administration of various drugs. The short-term administration of calcium, ascorbic acid, rutin and procaine were without effect, but an antihistamine (Synpen®) markedly reduced the edema and reflex erythema.

The patient improved greatly after several insulin shock treatments. This author questions the importance of histamine release in the pathogenesis of cold urticaria.

Sheldon[30] et al comment on unpublished work by them in which a similar technique to that used by Illig[13] was employed in studying a cold-sensitive patient. They found that the local inhibitory effect of antihistamine was equaled by atropine. Procaine was ineffective.

Mathov[21] in a study attempts to find a practical method for detecting the sensitivity of the respiratory system to the action of cold, to obtain an objective and easily carried-out test which will show the allergic character of the reactions, and to investigate the per cent of reactions to cold among a group of allergic patients. In forty allergic patients studied, 40 per cent claimed that the disorders were brought about by getting cold or wet but only 17 per cent showed objective symptoms (rhinitis, cough, asthma) with the test of immersion of hands in water at 0° Centigrade for ten minutes. The eosinophilic index, that is the difference between the eosinophil content in nasal mucus before and after the test, proved to be a most reliable and objective guide. The author contends that a large number of eosinophils in the nasal mucus of patients that reacted to cold shows that the respiratory symptoms are due to an allergic mechanism and not to a vasomotor reflex.

Mathov[22] also observed 100 workmen employed at the municipal meat packing factory of the city of Buenos Aires. Subjects were taken at random from those who work in the freezing chambers (temperature between —3° and —30° Centigrade) from one to six hours with intervals of rest between. Fifty-two per cent experienced certain symptoms when entering the freezing chambers. Eighty-one and four-tenths per cent of those who experienced symptoms showed an increase in the eosinophils in the nasal mucus when in the freezing chambers. Thirteen of the seventeen patients who showed allergy to cold were given an antihistamine and 100 per cent felt an improvement, either moderate or marked.

Rostenberg[28] as well as others have shown that the critical temperature at which symptoms develop varies considerably. It is apparent that there must also be a temperature gradient. Sudden drops in temperature during warm months will produce symptoms, yet the same temperature level in winter months will not produce a reaction.

A case of a white female child, four and one-half years old, with nonpruritic eruption involving cheeks, neck and exposed portions of the upper and lower extremities is reported by Rodin.[26] Observation revealed that lesions occurred only on exposure to cold and that usual length of exposure required was one-half hour. The eruption could be terminated by exposure to heat. Family history revealed this dermatosis to be present as a dominant non-sex-linked Mendelian trait. Sensitivity to cold was traced to twenty immediate relatives and antecedents. The question of this being a true allergy is raised, since there is a perfect family history of not similar but identical manifestations. If not a true physical allergy, it is postulated that this is a nonallergic type of disease produced by a genetic neurovasomotor disturbance. The demonstration of successful passive transfers in this case is questioned as lacking proof that these are on an antibody basis.

Witherspoon, White, Bazemore and Hailey[35] report a case, the third in the literature, of an extensive family history of urticaria due to cold. In all of the affected members of the family the condition appeared shortly after birth. Attacks were brought on in every case by cold, wind, or ex-

treme changes in temperature. The syndrome produced was characterized by urticarial wheals, lack of pruritus, presence of a burning sensation, pain and swelling of joints, chills and mild fever. These findings were similar to those previously reported. This case report was of a nineteen-year-old soldier in which there was an incidence of the identical syndrome in twenty-four out of forty-five members of his family for four generations.

Rodin and Bluefarb[27] report a case of cold urticaria in a four and one-half-year-old girl who was one of twenty-one cases of cold urticaria occurring in the family within four generations. All laboratory tests including passive transfer tests, cold agglutinations, cryoglobulin and Coombs test were essentially negative.

A case of hypersensitivity to cold with both local and generalized symptoms and with paroxysmal diarrhea complicating the reaction on several occasions is reported by McGovern.[23]

Harris[7] describes a new method for testing for cold and heat. He uses a disc 2 inches in diameter formed by coiling flat copper tubing. One end of the tubing is connected to a source of circulating hot or cold water. The other end goes to the wasteline with a thermometer intercepting. The disc is strapped or applied to the skin area to be tested. An ordinary mixing water faucet makes all gradations of temperature available.

A case of cold hypersensitivity is reported by Rothschild,[29] in which the effects of cold on blood pressure, gastric secretion, and local tissue were observed to be reversed after administration of Benadryl.® It is felt that this lends support to the hypothesis that the release of histamine-like substances is responsible for the symptoms in this condition.

LIGHT SENSITIVENESS

Kierland[18] calls attention to the fact that reactions of hypersensitiveness occur occasionally with roentgen, grenz and radium irradiation, in addition to the rays of the visible spectrum, and that it is important to note that certain instances of so-called photosensitiviy really are due to the heat of such energy rather than the light *per se.*

A new classification of cutaneous reaction to sunlight is given by Kesten and Slatkin.[17] Four categories are used. The first includes light sensitivity diseases occurring in apparently normal skin. In this category are included: (a) solar erythema, (b) chronic polymorphic light dermatitis, (c) solar urticaria, and (d) photodynamic dermatitis. The second category includes diseases occurring on skin that is presumably abnormal, such as in porphyria, hydroa vacciniforme, epidermolysis bullosa, xeroderma pigmentosa, et cetera. The third category includes diseases occurring as a Koebner phenomenon, such as pellagra, lupus erythematosus, papular urticaria and others. The fourth category includes diseases occurring in skin after prolonged exposure to sunlight, such as chronic sunburn with or without keratoses, epithelioma, and degeneration of collagen and elastic tissue. The use of light-transmitting filters for delineation of wave lengths in the solar spectrum producing sensitivity to light is discussed. They also give a good analysis of the use of sun screens. It would seem that ointments incorporating 15 per cent para-aminobenzoic acid give the best protection.

Lamb[19] et al present an accurate study of 145 cases of solar dermatitis. A new classification of polymorphic light-sensitive eruptions based on morphologically and clinically demonstrated variations is proposed. Photosensitivity on an allergic basis from foods and weeds was found to be extremely rare. The absence of porphyrinuria in their cases would seem to

eliminate these substances as photosensitizing agents in solar dermatitis. A possible explanation of the etiology of solar eczema on the basis of physical allergy is suggested by the fact that in a few of the patients an immune reaction to sunlight was observed. After the initial exposure in the spring to sunlight, a severe exacerbation of lesions occurred, but later in the summer only mild responses were evoked. Attention is called to the fact that fluorescent lighting is capable of both provoking and prolonging the eruption in light-sensitive individuals.

Kesten[16] presents a case of urticarial light sensitivity caused by wavelengths between 4000 and 5000 Å in which passive transfer of this sensitivity could be achieved. It is common to be able to demonstrate circulating antibodies in urticaria solare caused by wave lengths below 3700 Å, but whenever it is caused by rays above 3700 Å attempts at passive transfer have generally failed.

Fiedelsberger and Lindemayer[6] report two cases of hypersensitivity to light in which the Prausnitz-Küstner reaction was negative. Combined sun-ray and antihistamine treatment was successful in both cases.

Epstein[5] studied two cases of solar urticaria, one of them associated with purpura photogenica. Passive transfer tests were positive regardless of the difference of the spectral range. He finds that solar urticaria caused by violet and blue light does not seem amenable to treatment although spontaneous fluctuations of the sensitivity occur. Solar urticaria due to ultra violet light apparently can be helped more or less by antihistaminics.

Dainow[2] reports concerning two patients with a solar eczema of several years' duration, whose stools showed increased amounts of porphyrin. He attributes the excellent results obtained with Gantrisin® to the inhibition of porphyrin-producing *B. Coli* in the intestinal tract.

Harris[7] in testing for actinic rays uses an apparatus consisting of a cylindrical container with a geometric figure cut in the base. The light source is placed four inches above this opening. Ultraviolet, infra-red or ordinary bulbs may be interchanged for testing purposes. The opening at the base is placed directly on the skin area to be tested. Exposures are made at given time intervals. Filters may be used under the geometric opening to give narrower ranges of wave length.

HEAT ALLERGY

Kierland[18] found that treatment of heat-sensitive cases with so-called antihistaminic preparations occasionally alleviated an acute episode but it has not prevented the development of future attacks. Most satisfactory results were obtained by attempts at desensitization by means of immersing of a hand or forearm in water of gradually increasing temperature.

Sigel[32] reported twenty-two cases of urticaria caused by heat, exertion and excitement among American soldiers in Japan. Any cooling agent would give relief from symptoms. Histamine desensitization was ineffective.

Hellemans[8] reports studies of two soldiers, both with previous histories of allergy, who were subject to attacks of urticaria following physical strain. These attacks could be reproduced at rest by exposure to cold or hot showers. Antihistamines effectively relieved attacks. It is presumed that some disturbance in thermo-regulation occurred with exercise or exposure to heat or cold and that an abnormal histamine production followed and produced the urticaria.

Herlitz[9] described two cases of urticaria following physical exertion,

and implicated lactic acid as the causative allergen. Hyposensitization by injection of graded amounts of lactic acid is said to have been achieved and to have produced a beneficial therapeutic result.

MECHANICAL STIMULI

Rasmussen[25] studied the effect of antihistaminics on histamine whealing and on dermatographism. This was then elucidated by comparative electrophoretic experiments, and he concluded that the similarity of results obtained supported the theory that dermatographism is produced by liberation from injured cells of a histamine-like substance. This conclusion is similar to that of Urbach.

Marcussen[20] described a syndrome which he calls dermographic prurigo like lesions in areas of friction.

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630 Professional Building

THE SEARCH FOR ORALLY EFFECTIVE DRUGS TO PREVENT ASTHMA ATTACKS

Dr. John H. Biel, chief of the medicinal chemistry division of Lakeside Laboratories, described in the *Journal of the American Chemical Society* (76:3149, 1954) the search for an unusual drug which can protect the asthmatic patient against attacks even when taken orally. Present drugs have three limitations, he explained: (1) they are not effective orally; (2) they have side effects on the heart and blood vessels; and (3) they produce only temporary action after the actual onset of an attack and cannot be given prophylactically.

Studies are therefore being made to incorporate pressor amines into the arterenol molecule, and approximately sixty such bronchodilators have been synthesized and tested in guinea pigs against histamine- or metholyl-induced asthma. Several compounds have proved equal or superior to the most potent anti-asthmatic preparations now available, and several were as effective orally as parenterally, with prolonged action being demonstrated in some. However, Dr. Biel carefully pointed out that "Only clinical trial can establish the therapeutic usefulness of these agents in human asthma, which may be quite unrelated to artificially induced bronchospasm in guinea pigs."

In Memoriam

EDWIN G. FABER

Word has just been received of the death on December 8, 1954, of Dr. Edwin Gabriel Faber of Tyler, Texas, and it is with regret that we announce this to his fellow members in the College.

Dr. Faber was born in Titusville, Pennsylvania, on June 26, 1896. He received his education at the universities of Texas and Colorado, and was awarded his medical degree at the University of Colorado School of Medicine in 1919. After serving his internship at St. Luke's Hospital in 1919-20, he was resident physician at Children's Hospital in Denver, 1920-21. From 1925 to 1935 he taught at the University of Colorado School of Medicine, during which time he was also on the staffs of St. Luke's and Mercy Hospitals and was director of the outpatient department at the university from 1926 to 1928. At the time of his death he was a member of the attending staff of the Mother Francis Hospital in Tyler, Texas, being president of the executive staff in 1942 and chief of the department of medicine in 1946, serving this institution continuously since 1937 with the exception of the war years when he served in the U. S. Army with the rank of colonel. Dr. Faber was Clinical Assistant Professor of Medicine at Southwestern Medical School of the University of Texas from 1946 to 1953, when he resigned because of ill health. He was a member of the Smith County Medical Society, the Texas Medical Society, the American Medical Association, Southern Medical Association, the American Trudeau Society, was a diplomate of the American Board of Internal Medicine, and had served on the Board of Directors of the National Tuberculosis Association. He was elected a Fellow of the American College of Allergists in November 1943.

Dr. Faber is survived by his wife, Louise, and his son, John, of Tyler. To them and to his many friends the officers and members of the College extend their sincere sympathy.

FLORIDA ALLERGY SOCIETY

The seventh annual meeting of the Florida Allergy Society was held on Sunday, April 3, at the Vinoy Park Hotel, St. Petersburg, Florida, with Dr. Samuel D. Klotz presiding. Three subjects were discussed: (1) Pre-clinical investigations of possible allergens peculiar to sub-tropics and tropics: I. Pollens; (2) Studies in the endocrinopathic type of vasomotor rhinitis; and (3) Regional factors of importance in south Florida as related to allergy. Officers elected for the ensuing year are: President, Dr. W. Ambrose McGee; vice president and president-elect, Dr. Edwin P. Preston; and secretary-treasurer, Dr. Norris M. Beasley.

News Items

SECOND INTERNATIONAL CONGRESS OF ALLERGOLOGY

The Second International Congress of Allergology will be held under the auspices of the Brazilian Allergy Society in Rio de Janeiro, Brazil, November 6-13, 1955, with Dr. Fred W. Wittich presiding.

There will be a three-or four-day instructional course immediately preceding the meeting, under the direction of Dr. Leo Criep of Pittsburgh, Pennsylvania.

A commercial exhibit promoted by the Brazilian Allergy Society and sponsored by the Brazilian government and the International Association of Allergology will be held at the Hotel Quitandinha, the Congress headquarters, from November 1 through November 15. The exhibit will be located in a circular hall which will accommodate 100 exhibitors' booths, each measuring 6 x 10 feet. Any industrial or Commercial firm dealing with chemical or pharmaceutical products, medical or surgical equipment, et cetera, may have an exhibit and bring its products for this exhibition. All articles and merchandise brought into Brazil for this exhibition will be exempt from duties and taxes, will be in bond during the period of the exhibition, and will be re-exported after the show to their countries of origin. Those interested in renting space in this exhibition should write the Organizing Committee of the II International Congress of Allergology, Avenida Rio Branco, 277, 9° Andar, Grupo 904, Rio de Janeiro, Brazil, specifying the product or article they wish to exhibit, the quantity of each item and the space desired.

There will be a comprehensive program dealing with the most important problems of allergy, immunology, biochemistry, pharmacology, and therapeutics. Sir Henry H. Dale of London, Professor Pasteur Vallery-Radot of Paris, and Dr. Robert A. Cooke of New York have accepted invitations as special speakers. Others who have accepted invitations to participate in the Symposia include: Richard Schayer, A. E. Zeller, and S. M. Feinberg, Chicago; B. N. Halpern, Paris; E. A. Brown, Boston; R. L. Mayer, Summit, New Jersey; J. R. Marrack, London; C. Jiminez Dias, Madrid; G. Piness, Los Angeles; F. W. Wittich, Minneapolis; U. Serafini and C. Frugoni, Rome; C. Arbesman, Buffalo; B. Rose, Montreal; L. Schwartz, Washington; H. Storck, Zurich; J. Charpy, Marsielles; and Freund, New York.

The Symposia will cover such subjects as histamine, histamine liberators, allergy to drugs and antibiotics, immunology and allergy, the asthmatic patient, endocrines and allergy; therapeutics, allergy in tuberculosis and leprosy, allergy to microörganisms and parasites, and dermatologic allergy. Portuguese, Spanish, French, and English will be the official languages, and a phone interpreter system will enable each listener to hear the subjects presented in his native language.

A number of smaller sectional meetings will take place simultaneously for one and one-half days preceding the Symposia. Those who wish to participate in the sectional meetings should send a one-page abstract in triplicate, double spaced on thin paper, to Dr. F. W. Wittich, 424 LaSalle Building, Minneapolis, Minnesota, not later than July 31. Those wishing to discuss a particular type of topic but who do not wish to present a paper should also notify Dr. Wittich. Sectional papers will be given only in the language of the speaker.

Travel arrangements may be made through Braniff International Airways, Delta Steamship Line, Pan-American Airlines, or the Bankers' and Merchants' Travel

Service, and full packet information on the trip has been sent out by them. The approximate cost for the round trip from the United States will be $1,000. With very little added expense one can arrange a complete South American trip to include visits to Montevideo, Buenos Aires, Santiago and the Chilean Lakes, Lima, Bogota, and Panama.

A registration fee of $15 will be charged for the congress. Those who wish to register may do so by writing to the president, Dr. F. W. Wittich, 424 LaSalle Building, Minneapolis, Minnesota. Hotel rates and food in Rio are fairly inexpensive, and we are informed that the average costs, including room and meals, during the week of the congress will be $100. The Quitandinha Hotel, the Congress headquarters, although inexpensive, is one of the most famous tourist hotels in the world, located forty-five miles from Rio in the city of Petropolis. There will be shuttle bus service between the hotel and Rio, so there may be easy access to all the attractions of this area.

Besides the scientific meetings, the program will include receptions, excursions, entertainments, and banquets.

AMERICAN COLLEGE OF CHEST PHYSICIANS

The Twenty-first Annual Meeting of the American College of Chest Physicians will be held at the Ambassador Hotel, Atlantic City, New Jersey, June 1 through 5, 1955. The scientific program will include approximately 200 speakers representing specialists in all aspects of diseases of the heart and lungs. In addition to formal presentations, the program comprises a number of symposia, round table luncheon discussions, diagnostic-treatment conference and motion pictures, with more than the usual amount of time allotted for open discussion.

A new feature this year will be the Fireside Conferences, on Friday evening, June 3, at which more than thirty experts will be present to lead the discussions on as many subjects of current interest in the specialty of diseases of the chest.

Fellowship examinations will be held on June 2, and on Saturday evening, June 4.

All interested physicians are invited to attend; there is no registration fee. Copies of the program may be obtained by writing to the Executive Offices, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

SCHERING CORPORATION ANNOUNCES TENTH ANNUAL AWARD COMPETITION FOR MEDICAL STUDENTS

In keeping with its aim to encourage medical writing and exploration of current research literature, Schering Corporation announces the opening of its tenth annual Schering Award competition for medical students. This year papers are invited on three subjects: Current Concepts in the Management of Osteoporosis; Prevention and Treatment of Blood Transfusion Reactions; and Recent Trends in the Clinical Use of Adrenocortical Steroids. The contest is open to both American and Canadian medical students. A first prize of $500 and a $250 second prize will be awarded for each of the three subjects, and special recognition in the form of a professional gift will be given each student submitting a meritorious paper. Deadline for entry form indicating the choice of title is July 1, and manuscripts should be mailed not later than October 1. Information and instructions are available from the Schering Award Committee, 60 Orange Street, Bloomfield, New Jersey.

NEWS ITEMS

SCHERING AWARD WINNERS FOR 1954 ANNOUNCED

Awards of three $500 first prizes and three $250 second prizes in the Schering Award Competition for 1954 have been announced by Dr. Robert W. Burlew, chairman of the award committee. Recipients of the awards are as follows: Billy Franklin Andrews of Duke University, first prize, and George Alexander Wilson of Ohio State University, second prize, for papers on the subject, "Prophylactic and Therapeutic Uses of Parenteral Antihistamines." For papers on "Modern Treatment of Infections and Allergic Disorders of the Eye," first prize went to Richard Ellis Land of Northwestern University, and second prize to Alvin Lashinsky of New York University. Marvin Jerome Friedenberg of Tufts College Medical School won first prize, and Robert J. E. Zechnich of the State University of New York at Syracuse won second prize for papers on "Androgen Therapy in the Female."

ALLERGY-FREE PRODUCTS PURCHASES BUILDING

Allergy-Free Products, a sustaining member of the College, announces the purchase of its own building in Springfield, Missouri. At the new, larger quarters, they will manufacture Protecto-Dust Encasings, latex foam box springs, blanket covers, and tickings for latex foam products. The new building will have a special room for mixing hypoallergenic insecticide. All of the company's activities in Springfield will be carried on in the same building, but the company will continue its sales office in Brooklyn, New York. This move will not involve a change of address.

"HANDBOOK FOR THE ASTHMATIC" NOW AVAILABLE

A sixteen-page manual entitled "Handbook for the Asthmatic," published under the sponsorship of the American Foundation for Allergic Diseases, is now available from the Foundation office for twenty-five cents in coin. This booklet is non-technical and is written for the general public. Larger quantities are available at a reduced cost.

MEMBERSHIP ROSTER—AMERICAN COLLEGE OF ALLERGISTS

Additional copies of the 1955 Membership Roster of the American College of Allergists are available for $2.00 each at the College office, 401 LaSalle Building, Minneapolis 2, Minnesota.

AFAD MOVES TO NEW QUARTERS

Since February 1, 1955, the new address of the American Foundation for Allergic Diseases has been Room 1203, 274 Madison Avenue, New York 16, N. Y.

NEWS OF COLLEGE MEMBERS

Dr. Gordon J. McCurdy, otolaryngologist, announces his association with Dr. B. L. Melton, 605 Professional Building, Phoenix, Arizona.

BOOK REVIEWS

YEAR BOOK OF DRUG THERAPY. 1954-1955 Year Book Series. Edited by Harry Beckman, M.D., Director, Departments of Pharmacology, Marquette University Schools of Medicine and Dentistry, Milwaukee, Wisconsin. 592 pages. Chicago: The Year Book Publishers, 1955. Price $6.00.

Dr. Beckman, in this "desk encyclopedia" on therapeutic procedures, has made available to the physician a simple means of keeping posted on advances in applied pharmacology. In digests of 460 articles from world literature, the editor has made available for quick reference and easy reading 418 new and improved drug treatment measures for 212 disease conditions, including detailed prescriptions and dosage schedules. Many of these digests are followed by Dr. Beckman's editorial comments and personal evaluations.

Over one hundred case reports are included, in addition to fifty or more clinical and experimental studies. All fields of medicine in which drugs are used are covered, together with information on how drugs are being used, how to get better results from established drugs, and how to avoid dangers and pitfalls. In the light of worldwide experience as contained in the articles digested here, exact information is given about prescriptions, dosage, pharmacology, action, indications and contraindications, and toxic effects of the various drugs discussed. Eighteen pages are devoted to allergy and fifty to antibiotics and sulfonamides. Drug therapy in cardiovascular diseases, dermatology, endocrinology, gastroenterology, hematology, internal medicine, neuropsychiatry, obstetrics and gynecology, ophthalmology, otorhinolaryngology, pediatrics, surgery, and venereology is also presented. Sprue, obesity, and gallbladder disorders and drug therapy for these conditions are new subjects covered in the present Year Book.

In the introduction, Dr. Beckman reviews the outstanding developments in drug therapy in the past year. The very complete and well-organized index should be a help in finding required information readily.—V.E.S.

CURRENT THERAPY, 1955. Latest Approved Methods of Treatment for the Practicing Physician. Edited by Howard F. Conn, M.D. 692 pages. Philadelphia: W. B. Saunders Co., 1955. Price $11.00.

The seventh edition of "Current Therapy" brings to the practicing physician 692 pages of the latest, safest, and most effective treatment known to medical science today for over 400 diseases encountered in daily practice. All material has been written especially for this publication by 295 carefully selected contributors.

Nearly one hundred new treatments are described this year, but of necessity some important information has been repeated from previous editions, as radical changes are not made in the therapy of all conditions every year, but it is important that the physician know whether or not the treatment has changed. In some instances more than one method of treatment is given for a specific disease entity, as a difference of opinion may exist or there may be different conceptions of the disease. Discussion is not limited to drug therapy, but covers all types of therapeutic measures.

As this volume is designed strictly as an aid in therapy, no diagnostic procedures are included, it being assumed that a correct diagnosis has been made before treatment is instituted.

The volume is divided into sixteen sections covering the broad subjects of the infectious diseases; diseases of the respiratory, cardiovascular, digestive, endocrine,

urogenital, nervous and locomotor systems; diseases of the skin, blood and spleen; disorders of metabolism and nutrition; obstetric and gynecologic conditions; and diseases due to physical and chemical agents. Treatment of the various disease entities is described separately, briefly and completely under each heading. Accurate instructions are given, along with exact dosages and complete prescriptions when necessary.

The seventh edition is two hundred pages shorter than the last edition, and a number of disease entities previously discussed have been omitted from this revision; however, these states are relatively minor with a low incidence, and it is assumed that no advance in therapeutic measures has been made with respect to these conditions.—V.E.S.

ATLAS OF MEN. A Guide for Somatotyping the Adult Male at All Ages. By William H. Sheldon, Ph.D., M.D., Department of Medicine, College of Physicians and Surgeons, Columbia University; and the University of Oregon; with the collaboration of C. Wesley Cupertuis, Ph.D., School of Medicine, Western Reserve University, and Eugene McDermott, M.A., Dallas, Texas. 357 pages. New York: Harper & Brothers, 1954. Price $10.00.

This superbly produced volume, which is outsize and handsomely printed, is the fourth book to appear in the controversial "Constitutional Psychology" Series. The first two volumes, "Varieties of Human Physique" and "The Varieties of Temperament," were an attempt to correlate man's structure and personality.

In the present volume, the author sets up three major components of physique (endomorph, mesomorph, and ectomorph) and establishes a seven-point scale to cover the wide variation within each component. The commonest male somatotype is 443, that is, one who is graded 4 in endomorphy, 4 in mesomorphy, and 3 in ectomorphy, meaning that he is moderately fat, moderately muscular, and below the halfway mark in linear fragility. The book is replete with 1:30 body-build photographs of 1175 men in identical postures selected from a master file of 46,000, with age-height-weight norms for each of the 88 known "somatotypes," accompanied by verbal and graphic sketches of birds, insects, and mammals. These norms are an interesting and useful contribution to the subject, although there may be some controversy as to the method of computation. The interpretation of the material is independent, based on the author's own ideas.

In Part I, the author discusses the need for a biological identification tag, describes a pilot study including the effects of sex, age, and nutrition on the somatotype, and the problem of norms for weight, as well as individual differences within the somatotype.

Publication of this volume was made possible by funds granted by the Wenner-Gren Foundation for Anthropological Research. In spite of the long descriptions of types, "Atlas of Men" has a clear and concise style, and the photographs supplement the descriptions very well. The volume constitutes one of the most complete contributions to the classification and understanding of human individuals.—F.W.W.

FLUID THERAPY. James D. Hardy, M.S., M.D., F.A.C.S., Associate Professor of Surgery and Director of the Surgical Laboratories, Medical College of the University of Tennessee. 255 pages, illus. Philadelphia: Lea & Febiger, 1954. $5.50.

Rapid and satisfactory advances have been made in recent years in the knowledge of fluid and electrolyte metabolism, and thus the development of our knowledge of the value of supportive therapy in preoperative, operative, and postoperative management has been remarkable. The use of isotopes and other substances has

enabled us to measure the body fluid compartments and electrolyte pools, and has made it possible to study body fluid shifts in living subjects, thus improving our knowledge of supportive therapy.

In this succinct and practical book of 255 pages (including a very complete index), Dr. Hardy accomplishes his stated purpose of presenting a concise discussion of total fluid therapy. Throughout the book the major physiologic factors are examined, with the objective of providing factual clinical answers to the questions of *how much—of what fluid—by what route—how fast?* In the first two chapters the general physiology of all body fluid regulation and descriptions of certain laboratory procedures are presented. Following this, there is a simple, practical, and widely applicable approach to the management of clinical problems of fluid imbalance. Special attention is given to potassium depletion, management of intestinal obstruction, fluid therapy in pediatric practice, and problems related to the surgical specialties. There are discussions of acute and chronic renal failure, early treatment of burns, blood volume and management of blood loss, and liquid alimentation. The many complications involved in fluid therapy are described, and the common and significant reactions are explained. Each chapter is well illustrated with charts, graphs, and photographs, and is followed by a comprehensive list of references. The importance of using milliequivalents rather than milligrams or volumes per cent is emphasized, and a chapter is devoted to understanding of this measurement.

A practical understanding of fluid therapy by surgeons, surgical residents, interns and practicing physicians is required by modern procedures, and this subject is now an essential in the teaching of our medical schools. The physician constantly faces new patients who present new problems as to the best method of providing blood, water, electrolytes, calories and nitrogen in a volume of intravenous fluid that will not be excessive in amount for the individual patient. Such problems can be considered and solved with the sound and practical material found in this authoritative book.—F.W.W.

FLUID AND ELECTROLYTES IN PRACTICE. Harry Statland, M.D., Associate in Medicine, University of Kansas School of Medicine; Consultant in Medicine, Veterans Administration Hospital, Kansas City, Missouri; Attending Physician, Menorah Medical Center, Kansas City, Missouri. 206 pages. Philadelphia: J. B. Lippincott Company, 1954. Price $5.00.

This author has reworked and elaborated a lecture series presented at the University of Kansas School of Medicine into the present volume to give the material permanent form. He aims at a thorough coverage of present knowledge of this important aspect of medical and surgical therapy, emphasizing its practical application in clinical situations.

The book is in two parts. Part I deals with general principles, such as fluid structure; movements of fluids in the body; intake, output and variations; prevention of imbalance in the postoperative patient; water and salt depletion; mixed depletions, potassium alterations and magnesium; acid-base balance, treatment of major depletions; and edema, diuretics, and water intoxication. In Part II, the author applies these principles to such special conditions as heart disease, kidney and urologic diseases, diabetic acidosis, pediatric fluid balance, burns, cirrhotic ascites, and toxemias of pregnancy, with practical clinical suggestions concerning the fluid requirements, electrolyte administration and other measures during the various phases of disease states.

This is a very practical book for both the medical student and the physician who realizes the importance of fluid and electrolyte metabolism and wishes to keep abreast of present-day treatment.—F.W.W.